KETAMINE: ITS PHARMACOLOGICAL INTERACTIONS WITH HALOTHANE ANESTHESIA

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TO LINDA:

For lovingly sharing my ups and downs...

...we finally made it!

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KETAMINE:

ITS PHARMACOLOGICAL INTERACTIONS WITH HALOTHANE ANESTHESIA

Ketamine was introduced as a rapid, short-acting parenterally administered anesthetic and it often is used clinically to induce anesthesia prior to administration of inhalation anesthetics (e.g. halothane). Despite claims for a short duration of action, a prolonged recovery frequently is observed with this combination of anesthetic drugs. The present study questioned if the effect of ketamine were indeed evanescent and also whether the concomitant administration of halothane prolonged the effects of ketamine. Thus, the effects of ketamine and its principal metabolite, metabolite I, on the halothane anesthetic requirement (i.e. MAC) were studied in male S.D. rats. Additionally, the effects of halothane anesthesia on ketamine biodisposition were evaluated with respect to both pharmacodynamic and pharmacokinetic processes.

Ketamine's pharmacologic actions were shown to include hypnosis, analgesia and ataxia. Metabolite I appeared to produce identical pharmacological actions via a similar mechanism(s), although it was significantly less potent than the parent compound. The duration of ketamine's posthypnotic actions were influenced to varying degrees by alterations in its hepatic metabolism. Repetitive administration of ketamine caused reductions in the duration of its posthypnotic effects similar to those seen with agents known to stimulate hepatic metabolism of ketamine. In addition, chronic ketamine administration may lead to the development of pharmacodynamic "tolerance" to posthypnotic events (e.g. analgesia).

Both ketamine and metabolite I depressed halothane MAC in rats in a dose-dependent fashion. Even subanesthetic doses of ketamine resulted in depression of the CNS, as reflected by a decreased anesthetic requirement, for as long as six hours. Reduction in MAC correlated with brain levels of ketamine or

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metabolite I and suggested a ketamine/metabolite I potency ratio of 3:1 . It was concluded that ketamine is not a short-acting drug and that protracted recovery following ketamine administration is related to persistence of ketamine itself as well as to the formation of an active metabolite.

Biodisposition studies of ketamine in the rat demonstrated rapid distribution into highly vascular organs and subsequently redistribution to less-well perfused tissues, with concurrent hepatic metabolism and urinary and biliary excretion. Halothane, a potent cardiovascular depressant, prolonged the plasma and brain half-life of ketamine and also increased the duration of ketamine-induced ataxia when the two drugs were administered concomitantly. Surgical levels of halothane anesthesia decreased the rate of uptake and delayed distribution and redistribution of intramuscularly administered ketamine. Similarly, halothane altered the distribution and slowed the redistribution of intravenously administered ketamine. Furthermore, clinically useful concentrations of halothane decreased the overall rate of *in vivo* ketamine metabolism in a dose-dependent manner. Halothane noncompetitively inhibited *in vitro* hepatic microsomal metabolism of ketamine and metabolite I with inhibitor constants (Ki) for halothane of 1.56 and 1.64 mM, respectively. In the absence of halothane, the maximal velocity (Vmax) for the oxidation of metabolite I was only 44% of Vmax for the N-demethylation reaction under similar conditions. Thus, halothane anesthesia by decreasing uptake, distribution, redistribution and metabolism of parenterally administered ketamine significantly prolonged ketamine's action. Renal elimination is the major route of excretion for ketamine and its metabolites, however it does not play a significant role in ketamine's initial biodisposition and was not altered by halothane anesthesia. Although significant amounts of ketamine and its metabolites were excreted in bile, fecal excretion is of minimal importance in ketamine's overall biodisposition because of the apparent enterohepatic circulation of the lipid-soluble drug.

In conclusion, both ketamine and metabolite I are responsible for the post-hypnotic lethargy noted clinically after recovery from the anesthetic effects of ketamine. Further, inhalation anesthetics which depress the cardiovascular system and impair hepatic metabolic function may hinder the disposition of another drug given concomitantly. This type of interaction prolongs the therapeutic effects, as well as the undesirable side-effects, of a fixed agent like ketamine and would be expected to further contribute to the prolonged recovery from ketamine. Hence, both pharmacodynamic and pharmacokinetic mechanisms are involved in the drug interactions between ketamine and halothane.

CHAPTER I

GENERAL INTRODUCTION

KETAMINE

Intravenous anesthesia was first introduced into clinical practice with thiopental over forty years ago (Lundy, 1935). The thiobarbiturates, with thiopental as the prototype, are widely used as induction agents because of their rapid onset and short duration of action. The less desirable aspects of their use include increased sensitivity to somatic pain (Dundee, 1960), limitations on the route of administration, and the fact that large doses are needed to obtund reflex responses to surgery when this agent is used as the main or sole anesthetic. Thiobarbiturates can also cause profound circulatory and respiratory depression such that they are relatively contraindicated as the sole anesthetic agent in the aged as well as in the presence of hypovolemia. Furthermore, termination of thiopental's anesthetic action appears to result primarily from redistribution as it is slowly metabolized by the liver and excreted via the kidney, with a substantial proportion of a given dose remaining in body tissues (i.e. fat) following recovery from its anesthetic effect. The potential for drug interactions and cumulative dose effects is obviously increased because of the long non-neural tissue half-life.

The need for a safe, potent and short-acting parenterally administered anesthetic which combined analgesic and sleep-producing effects without significant cardiovascular or respiratory depression led to the clinical evaluation of the phencyclidine compounds. Preliminary clinical studies by Greifenstein et al, (1958) on the clinical usefullness of phencyclidine as an anesthetic showed that although it produced an adequate anesthetic state in most patients, its undesirable and occasionally long-lasting psychotomimetic activity during the post-anesthetic period precluded its widespread clinical acceptance.

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As a result of a search to find an analog of phencyclidine that would provide adequate surgical anesthesia and rapid recovery without its prominent psychotomimetic properties, ketamine (2-(o-chlorophenyl)-2(methylamino)-cyclohexanone HCl), initially referred to as CI-581, was synthetized in 1961. Ketamine was introduced as an agent capable of producing a unique anesthetic state unlike the common inhalation and injectable anesthetics. It was characterized as a state of catalepsy where the eyes remained open with a slow nystagmic gaze, corneal and light reflexes remained intact, and where varying degrees of hypertonus and occasional seemingly purposeful movements unrelated to painful stimuli were noted in the presence of surgical anesthesia (Domino, 1965). The so-called "dissociative anesthetic state" produced by this agent was described as a functional dissociation between the thalamo-neocortical and limbic systems where profound analgesia was coupled with a somnolent state in which the subject did not appear to be anesthetized but rather "disconnected" from the surrounding environment (Corssen et al, 1968).

Preliminary observations indicated that ketamine had a shorter, more controllable duration of action and less propensity for inducing seizures and severe emergence phenomena, while possessing similar analgesic and anesthetic properties as the chemically related phenylcyclohexylamine compounds (McCarthy et al, 1965). Domino et al (1965) in studies on human volunteers confirmed that ketamine would be more suitable than its parent drug for clinical anesthesia. The early clinical experience with ketamine indicated that it produced transient but minimal depression of respiratory function, elevation of both systolic and diastolic blood pressure, and occasional emergence reactions in adults consisting of a transient phase of vivid dreaming with or without psychomotor activity and manifested by confusion, changes in mood and affect, irrational behavior and hallucinations (Domino et al, 1965; Corssen & Domino, 1966). These later psychotomimetic side-effects appeared to be controllable by avoiding early verbal and tactile stimulation and with administration of small doses of short-acting sedative-hypnotic drugs (Corssen et al, 1968; Lotfy et al, 1970). According to data compiled by the manufacturer from over 1500 cases, the most common complications were; transient abnormal changes in blood pressure or heart rate (13%), emergence phenomena including delirium, euphoria, hallucinations, disturbances of body image and numbness (7%), inadequate pulmonary gas exchange secondary to mechanical causes, i.e. increased secretions and/or obstruction of the upper airway (5%), and finally, seemingly purposeful movements of the extremities, vomiting and post-anesthetic complications (3%). Thus, the major undesirable characteristics of the drug included the production of hypertension, tachycardia and occasional psychic changes.

Ketamine was initially advertised to be a potent, rapid and short-acting parenterally administered anesthetic with profound analgesic properties outlasting the duration of unconsciousness. It was considered to be use in brief diagnostic and surgical procedures, especially in children where psychic aberrations were uncommon (Roberts, 1967; Corssen et al, 1969; Wilson et al, 1969a). A further advantage of ketamine in pediatric anesthesia was that induction could be accomplished with one intramuscular injection and transition to general anesthesia was smooth and accompanied by stable vital signs and spontaneous ventilation. Ketamine has been found to be highly useful in radiotherapy in order to overcome the difficulty of providing adequate sedation and anesthesia without the continual presence of an anesthetist inside the irradiation area (Cronin, 1972; Bennett & Bullimore, 1973; Amberg & Gordon, 1976). Ketamine was also employed with good results in patients undergoing repeated anesthesia for debridement and grafting of acute burns and reconstructive plastic surgery for removal of burn contracture scars, without tolerance development

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(Wilson et al, 1969b; Feingold & MacMahon, 1975).

After extensive clinical investigation, including nearly 20,000 anesthetic administrations, ketamine (Ketalar) was approved by the FDA in 1970. The clinical uses for which ketamine was initially recommended included; (1) brief minor surgical and diagnostic procedures that did not require skeletal muscle relaxation (e.g. incision and drainage of abcesses, myringotomy, debridement and dressing of burns, bronchoscopy, GI tract endoscopy, cystoscopy, cardiac catherizations, and various otorhinolaryngology, opthalmologic and neuroradiologic procedures), (2) induction of inhalation anesthesia where the intramuscular route of administration was preferred or when an ultrashort-acting barbiturate was contraindicated or avoidance of cardiovascular depression critical, and (3) to supplement low-potency agents (i.e. nitrous oxide). The Medical Letter (1970 & 1972) similarly recommended ketamine as an induction agent for patients in whom avoidance of cardiovascular depression was critical but not as the sole anesthetic for major surgery. Its psychomimetic effects (e.g. delirium, nightmares, hallucinations and schizoid reactions) were felt to be much more serious than with other conventional inhalation anesthetics. More recently suggested indications for ketamine have included the treatment of intractable hiccups (Shantha, 1973) and asthma (Corssen et al, 1972). Ketamine by virtue of its analgesic potency, wide margin of safety and relative lack of respiratory depression, has been recommended for treatment of postoperative pain which often restricts respiratory efforts and predisposes toward pulmonary complications (Clausen et al, 1975). Finally, the analgesic effects of ketamine administered in subanesthetic doses might provide useful in short manipulative procedures (i.e. closed reduction of fractures or joint manipulations) or in situations where narcotic analgesic agents are contraindicated. Nevertheless, ketamine's use in adult patients remains very controversial because of the reportedly high incidence of undesirable side-effects associated with induction and emergence (King & Stephen, 1967; Dundee et al, 1970 & 1971; Morgon et al, 1971; Winters, 1972b). Other investigators have reported on its use with minimal complications (Corssen et al, 1968; Oduntan & Gool, 1970; Lorhan & Lippmann, 1971; Sanchez et al, 1971; Magbagbeola, 1971; Little et al, 1972; Walker, 1972; Klose & Peter, 1973; Langrehr & Neuhaus, 1973; Bidwai et al, 1975; El-Naggar et al, 1975).

Pharmacological studies:

Whereas conventional anesthetic agents result in cardiovascular depression, ketamine's transient hemodynamic effects appear to be a resultant of both inhibitory and excitatory actions. According to Taber et al (1968 & 1970), ketamine has both indirect stimulatory and direct depressor effects on the cardiovascular system, with the former predominating at low doses. At higher doses and in the absence of both sympathetic and vagal control, the elevations in heart rate, blood pressure and cardiac output were diminished through a direct depressor effect of the drug on the myocardium (Traber et al, 1968; Treese et al, 1973; Schwartz & Horwitz, 1975). The elevations in heart rate, blood pressure and cardiac output were abolished after premedication with a ganglionic blocker. It was further postulated that residual pressor responses produced by ketamine after muscarinic blockade were mediated via the sympathetic nervous system. Furthermore, the absence of a significant effect by β-adrenergic blockade on the cardiovascular response to ketamine implied that neither sympathetic innervation to the heart nor circulating endogenous catecholamines were responsible for its cardiostimulatory effects. It was concluded that ketamine increased α-adrenergic discharge and reduced vagal discharge to the heart such that, in the absence of sympathetic and vagal influence, the drug exerts a negative inotropic effect on myocardial contractility. Cardiovascular studies in humans by Kreuscher & Gauch (1967) and Virtue et al (1967) indicated that the pressor response observed during induction of anesthesia with ketamine was due primarily to an increased cardiac output.

It was originally hypothesized that ketamine inhibited baroreceptor function of carotid sinus nerves and thereby reduced the negative feedback mechanisms by which the cardiovascular system is regulated, with resultant arterial hypertension through central automonic stimulation. Dowdy & Kaya (1968) and others (Pender, 1971; Tweed et al, 1972; McGrath et al, 1975) found that ketamine did not inhibit the central baroreceptor pathway regulating sympathetic discharge. In studies on the cardiovascular effects of centrally administered ketamine, Ivankovich et al (1974) reported immediate increases in heart rate, blood pressure and cardiac output which were blocked by pentobarbital, indicating that the peripheral sympathomimetic effects were produced primarily by direct stimulation of the central nervous system (CNS). Other investigators (Chodoff, 1972; Clenachan & McGrath, 1975) have evidence to support the hypothesis that ketamine directly stimulates the central adrenergic centers. Still other studies indicate that ketamine has a peripheral cocaine-like effect of inhibiting neuronal uptake of catecholamines and thereby, altering adrenergic neuroeffector transmission (Takki et al, 1972; Nedergaard, 1973). Miletich et al (1973) reported evidence which supports the hypothesis that ketamine stimulates the cardiovascular system via both direct stimulation of the central adrenergic center(s) and indirectly by inhibiting neuronal uptake of catecholamines.

Ketamine has been found to produce a significant decrease in coronary sinus oxygen content despite an increase in coronary artery blood flow (Folts et al, 1975), indicating an increase in myocardial oxygen consumption. Ketamine has also been shown to cause increased cerebrospinal fluid (CSF) pressure, and presumably intracranial pressure, secondary to increased cerebral blood flow (Dawson et al, 1971; Gardner et al, 1971; Evans et al, 1971; Shapiro et al, 1972; Takeshita et al, 1972).

Respiration was not markedly altered by ketamine, although depression in minute ventilation often occurs immediately after parenteral administration of a large dose of the drug (McCarthy et al, 1965; Corssen & Domino, 1966; Pender, 1971; Coppel & Dundee, 1972). The mild respiratory depression produced is rapidly followed by a return to baseline ventilatory volumes, without loss of carbon dioxide responsiveness (Virtue et al, 1967). However, Folts et al (1975) have reported a significant decrease in minute ventilation when ketamine was administered following induction of anesthesia with a sedative-hypnotic/narcotic mixture. Various investigators (Wilson et al, 1967; Virtue et al, 1967; Doubrava & Larson, 1971; Lanning & Harmel, 1975) have noted preservation of pharyngeal and laryngeal reflexes with maintenance of an adequate airway without intubation. Nevertheless, tracheal soiling and aspiration has been reported after ketamine induction (Penrose, 1972). Ketamine also stimulates salivary gland secretions which must be blocked by an anti-sialagogue (Lanning & Harmel, 1975). Respiratory airway resistance was not altered by ketamine, although it did decrease the overall chest compliance (Watemath & Bergman, 1974).

Since phencyclidine did not markedly alter the cardiovascular or respiratory centers, Chen et al (1959) postulated that the drug exerted it anesthetic action principally in regions above the medulla in the midbrain region in contrast to the barbiturates which appear to act on the "reticular formation." Electroencephalographic (EEG) studies during ketamine anesthesia have been interpreted to imply that sensory impulses might indeed reach the cortex, but that they are not perceived because of depression of the association areas of the brain

(Corssen & Domino, 1966; Corssen et al, 1968). Ketamine appeared to depress the somatosensory association areas and subcortical structures while producing only minimal effects on the reticular formation and the limbic system. Using electrophysiological techniques, Miyaska & Domino (1968) presented evidence that would indicate an action of ketamine on the nonspecific thalamo-neocortical projection system, depressing corticothalamic system by interrupting sensory input at the level of the diencephalon as well as at association areas of the cortex. Prominent theta-wave activity was observed continuously during ketamine anesthesia, and there appeared to be a relationship between this type EEG activity and analgesia (Corssen et al, 1969). It was further postulated that the analgesic state may result from a functional block of ascending reticular pathways carrying the affective-emotional components to the non-specific midbrain and thalamic nuclei (Sparks et al, 1973) as well as via lamina specific suppression of neuronal activity at the spinal cord level (Conseiller et al, 1972; Kitahata et al, 1973; Sparks et al, 1975). This concept of a differential action of ketamine on various parts of the CNS has been disputed by Winters (1972a &b) and others (Kayama & Iwama, 1972; Wong & Jenkins, 1974) based on EEG evidence which indicated that the unconsciousness produced by ketamine was secondary to subclinical cortical seizure activity in both the thalamic and limbic systems which they termed "functional disorganization." Although ketamine has been demonstrated to be ineffective against strychnine-induced seizures, it was able to abolish electrically-induced tonic extensor and pentylenetetrazol-induced clonic seizures (Chen et al, 1966).

Since changes in the metabolism of CNS neurotransmitters have frequently been associated with the administration of psychotropic drugs, it is of interest that ketamine produced increases in brain c-AMP (Dedrick et al, 1975), acetylcholine (Cohen et al, 1974), serotonin and dopamine while concomitantly decreasing norepinephrine (Sung et al, 1973). Furthermore, Hatch (1973) was able to prevent ketamine-induced catalepsy and enhance ketamine anesthesia by pretreatment with an anti-serotonin neuroleptic agent, suggesting that serotonergic mechanisms may function to partly offset or adapt to the depressant effects of ketamine.

Toxicological studies:

In early animal studies, ketamine was found to produce a spectrum of action from excitation and ataxia to catalepsy, analgesia and anesthesia to convulations, and finally respiratory depression and death (Chen & Bohner, 1965). The signs of acute toxicity in rats include initial excitement and irritibility, rapidly followed by depression, severe incoordination and prostration with recovery occurring in a reverse sequence (Kaump et al, 1969). The LD50 in rats varied from 59 mg/kg following IV administration, to 224 mg/kg following IP injection, to 447 mg/kg following oral ingestion. The LD50 also was found to increase with age. Ketamine can be administered both intramuscularly and intravenously without significant tissue irritation or local vascular damage at the site of repeated injections. Long-term toxicity studies indicated no significant clinical findings except for a moderate depression in normal weight gain and slightly abnormal liver function tests, but neither gross nor microscopic organ damage was demonstrable (Corssen & Domino, 1966).

Clinical studies:

In a series involving over 400 administrations to children with burns for debridement and dressing changes (Wilson et al, 1967 & 1969b), ketamine was found to produce a slight rise in blood pressure, heart rate and respiratory rate (with a slight increase in tidal volume) consistent with a stimulatory effect

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on both the cardiovascular and respiratory systems. In these studies and others (Corssen & Oget, 1971; Bovill & Dundee, 1971; Sadove et al, 1971a; Slogoff et al, 1974) both anesthetic and subanesthetic doses of ketamine produced satisfactory analgesia, complete amnesia, and good operating conditions. They reported minimal respiratory depression, retention of the protective reflexes and prompt recovery with resumption of oral alimentation.

The use of intramuscular ketamine for radiotherapy in young children was reported to produce anesthesia with a predictable duration of action, sedation was not accompanied by obvious respiratory depression or depression of the protective reflexes, and recovery was rapid at the end of the treatment period (Cronin et al, 1972; Bennett & Bullimore, 1973). Although a slight rise in blood pressure and heart rate was commonly seen, emergence delirium and catatonia were uncommon in children. In these studies, tolerance to ketamine appeared to develop in the majority of children receiving daily radiotherapy for a continuous period of several weeks.

In children with congenital heart disease undergoing cardiac catheterization, the only cardiorespiratory changes noted after ketamine administration were increases in blood pressure and pulse rate (Stanley et al, 1968). In a study on the use of ketamine in patients undergoing cardiac surgery, Sanchez et al (1971) found that ketamine provided excellent deep analgesia with remarkable arterial pressure stability, minimal loss of muscle tone and preservation of the laryngo-tracheal reflex. The only problems reported were slightly increased salivation and post-operative hyperthermia.

The use of ketamine as an obstetrical anesthetic agent was suggested because of its rapid induction with profound analgesia, low incidence of nausea and vomiting, minimal effect on labor and excellent post-partum uterine contractility. In extensive clinical studies by Little et al (1972) and Langrehr &

Neuhaus (1973), ketamine was found to be a highly effective agent for both mother and fetus with no unexpected complications, and all side-effects (salivation, nausea, increased respiratory rate and vivid dreams) were mild except for the signigicant increases in blood pressure and pulse rate.

In a large study, Oduntan & Gool (1970) reported excellent results with ketamine and felt that it provided "a greater margin of safety than conventional anesthetics in poor risk patients." Intravenous ketamine was reported to produce rapid analgesia and anesthesia with a short duration of action and a brief post-operative recovery period. Although tachycardia and mild hypertension were usually produced, no evidence of respiratory depression or serious complications were reported apart from restlessness (8%) and hallucinations (8%). Other investigators (Lorhan & Lippmann, 1971; Nettles et al, 1973; Barson & Arens, 1974) have also reported rapid and effective surgical anesthesia in the aged "poor risk" patient, where the only physiologic alterations following ketamine administration were rises in blood pressure in patients with generalized atherosclerosis and slight hypotension and modest increase in heart rate in patients who were hypovolemic.

In a recent study, El-Naggar and associates (1975) reported that their patients experienced no excitation, hallucinations or psychosis, denied awareness of the surgical procedure and unnecessary discomfort or bad dreams, and experienced profound amnesia for events in the immediate post-anesthesia period. However, in the absence of depressant premedicants, the incidence of pre-operative retrograde amnesia with ketamine has been reported to be negligible (Pandit et al, 1971).

The clinical experience of Morgan et al (1971) with ketamine as the sole anesthetic for minor surgical procedures revealed that it produced adequate anesthesia in the majority of patients, however, there was a high incidence of elevations in blood pressure, hypertonus and purposeless movements during surgery as well as occasional inadequate analgesia and vivid dreams in adults. Although Dundee et al (1970 & 1971) reported generally satisfactory results with ketamine, emergence excitement occurred in almost one-third of their adult patients. Severe delirium occurred in less than 10% with lower inducing doses (i.e. less than 3 mg/kg) but increased to 24% when larger doses were given during induction of anesthesia. Given that ketamine can induce transient bizarre behavior patterns (including psychotic-like reactions) during emergence, there is no evidence from conventional psychological testing to support the supposition that ketamine induces permanent psychological changes (Corssen et al, 1971). Overall, unpleasant dreams have been reported in 2-30% of patients undergoing ketamine anesthesia and they are thought to be related to misinterpretations of visual stimuli resulting from nystagmus and a "sense of bodily detachment (Fine & Finestone, 1973)." Although the psychic manifestations of ketamine reportedly have visual disturbances as their basis, covering patient's eyes in the recovery room only reduces the incidence of dreams marginally (Hejja & Galloon, 1975).

Adjuvants such as anticholinergics, narcotics, sedative-hypnotics and tranquilizers (Bovill et al, 1971; Sadove et al, 1971b; Becsey et al, 1972; Loers, 1973; Coppel et al, 1973; Rita & Seleny, 1974) as well as inhalation anesthetic agents (Bidwai et al, 1975), have been only partially successful in reducing the incidence of random involuntary motor activity and emergence reactions. In a study on the effect of nitrous oxide during ketamine anesthesia, Wessels et al (1973) found that nitrous oxide reduced the required dosage of ketamine by 34% and recovery time by 63%, as well as improving operating conditions and patient acceptability. In spite a reduction in the incidence of its psychomimetic effects with adjuvant drugs, the bad dreams and delirium frequently associated with ketamine administration have prevented its wider use in adults. The drug available commercially (i.e. Ketalar or Ketaject) is a racemic mixture of ketamine and, since optical isomers often have differing potencies and pharmacolgic effects (Casy, 1970), clinical evaluation of the individual enantiomers might prove to be a more effective approach to solving the problem of emergence reactions following ketamine anesthesia.

Case reports regarding infrequently occurring problems associated with ketamine anesthesia have discussed the possible development of a progressive polyneuropathy (Cherington, 1970), ketamine-induced apnea secondary to increased intracranial pressure with medullary compression (Rapkin, 1971; Evans, 1971; Lockhart & Jenkins, 1972), generalized extensor spasm (Radnay & Badola, 1973) and a grand mal seizure (Thompson, 1972), postoperative hypercarbia with reanesthetization (Janis et al, 1972), increased intraocular pressure (Corrsen & Hoy, 1967; Yoshikawi & Murai, 1971), and severe hypertension and arrhythmias in a patient on thyroxine (Kaplan & Cooperman, 1971). Other rare complications of ketamine include severe laryngospasm with airway obstruction, vomiting with aspiration and hysterical postanesthetic reactions in children (Sears, 1971). Although ketamine has been used for induction and maintenance of general anesthesia without respiratory assistance or oxygen administration, Zsigmond et al (1976) reported arterial hypoxemia which would be clinically significant in patients with anemia and/or reduced cardiopulmonary reserve.

HALOTHANE ANESTHESIA

Since Sir J. Y. Simpson (1847) introduced chloroform as a clinical anesthetic, halogenated hydrocarbons have played an ever increasingly important role in clinical anesthesia. Halothane (CF3-CHClBr) was synthesized by Suckling, investigated by Raventos (1956), and introduced into clinical anesthesia by Johnstone (1956). Halothane has been the most widely used inhalation anesthetic in the western world over the last decade and its clinical uses and pharmacologic actions have been studied extensively, including several reviews and monographs (Johnstone, 1961; Stephen & Little, 1961; Sadove & Wallace, 1962; Greene, 1968; Ngai, 1972) as well as the the National Halothane Study (1969).

Halothane is an easily vaporized liquid at room temperature, is potent at low concentrations, has a pleasant odor, and is nonflammable. Induction of anesthesia with halothane is easily achieved either by direct inhalation or after inducting doses of thiopental or ketamine. There is early obtundation of pharnygeal and laryngeal reflexes before upper airway obstruction, minimal irritation of the larynx and trachea, and no noticeable increase in bronchial secretions. Halothane has a moderately high blood/gas partition coefficient (Larson et al, 1962) which retards equilibration and slows induction; however, its speed of induction is hastened by using high concentrations during the induction period. The depth of anesthesia can be rapidly altered (although the classical Guedel signs of ether anesthesia are absent) and emergence from halothane anesthesia is usually smooth with a low incidence of nausea and vomiting and an absence of lingering effects. The moderately high lipid solubility of halothane often results in its accumulation in body fat depots which tends to produce a somewhat protracted recovery. Furthermore, the tendency of halothane to cause hypotension at deeper levels of anesthesia and its lack of analgesic potency (Houghton et al, 1973) has discouraged its use as a primary anesthetic agent. In the vast majority of cases, halothane is administered in low concentrations in conjunction with a thiobarbiturate, nitrous oxide and a neuromuscular blocking agent to produce a smooth course of light surgical anesthesia (i. e. so-called balanced anesthesia technique). Its undesirable pharmacologic properties include concentration-dependent cardiovascular and respiratory depression (Deutsch et al, 1962; Black & McKane, 1965; Eger et al, 1970), as well as a rare hepatotoxic effect which is more likely to occur following repeated administrations (National Halothane Study, 1969). Relative contraindications to the use of halothane include infants (less than one year of age), patients in shock and patients who have recently undergone halothane anesthesia. Finally, the administration of halothane requires specially trained personnel and constant monitoring of the patients status.

Pharmacological studies:

Halothane depresses cardiovascular function via both central and peripheral hemodynamic actions. It decreases efferent sympathetic nervous system activity (Price et al, 1963; Skovsted et al, 1969) and also interfers with neuronal transmission at the sympathetic ganglion (Biscoe & Millar, 1966). Systemic arterial blood pressure, myocardial contractility, cardiac output and total peripheral resistance are all reduced by halothane at anesthetic concentrations (Deutsch et al, 1962). Although the reduction in cardiac output is chiefly the result of a reduction in stroke volume rather than heart rate, halothane does cause direct depression of the S-A node (Flacke & Alper, 1962; Hauswirth & Schaer, 1967). Halothane also "sensitizes" the ventricular conducting tissues to the action of catecholamines (Andersen & Johansen, 1963). Nevertheless,

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most arrhythmias occurring during halothane anesthesia are associated with hypercarbia and hypoxia secondary to respiratory depression. Halothane increases cerebral blood flow primarily via a direct vasodilator action on vascular smooth muscle (Wollman et al, 1964) and this results in an elevation of CSF pressure (Marx et al, 1962). It also produces vasodilatation in skin and skeletal muscle (Black & McArdle, 1962). In the splanchnic and renal circulation there are no consistent changes in vascular resistance (Epstein et al, 1966) such that the decline in blood flow is proportional to the degree of hypotension produced. There also is evidence that tolerance develops to the circulatory actions of halothane during continued exposure (Eger et al, 1970).

Halothane produces significant depression of ventilation with a marked reduction in tidal volume and carbon dioxide-responsiveness at alveolar concentrations compatible with light levels of surgical anesthesia (Schaefer, 1958). The resulting increase in the arterial carbon dioxide level and the decreased slope of the CO2-response curve are proportional to the alveolar concentration of halothane and therefore, to the depth of anesthesia. If adequate ventilation is desired, ventilation must be assisted during light levels of halothane anesthesia and controlled at deeper levels. Entubation is easily accomplished under halothane anesthesia because it relaxes the masseter muscles, inhibits salivation and obtunds laryngeal and pharyngeal reflexes. Laryngospasm, bronchospasm and coughing are all inhibited by halothane. However, the ability of halothane to produce bronchodilation has been disputed (Patterson et al, 1968; Waltemath & Bergman, 1974).

Halothane decreases mucous glandular secretions, relaxes gastrointestinal smooth muscle and inhibits GI motility (Marshall et al, 1961). Halothane also reduces myometrial tone in the gravid uterus (Embrey et al, 1958). Although its skeletal muscle relaxing properties are poor, halothane does produce a neuromuscular blocking action via CNS depression of both spontaneous efferent discharge and reflexly-induced motor activity (Ngai et al, 1965). Halothane also appears to sensitize the peripheral mechanoreceptors, including the pulmonary stretch receptors and carotid baroreceptors (Whitteridge, 1958).

Halothane is thought to work primarily by depressing the secondary afferent systems (i.e. the reticular activating system of the brainstem) to reduce the input to the cerebral cortex, although it also depresses subcortical structures that regulate somatic and visceral functions (Davis et al, 1961). The EEG changes during halothane anesthesia show the characteristic pattern of disappearance of α-rhythm with initial loss of consciousness and a fast rhythm with a low voltage during light anesthesia. With increasing depth of anesthesia, the EEG changes to a slow rhythm with high voltage (i.e. theta activity) followed by periods of burst suppression interspersed with slow activity of reduced voltage (Gain, 1957). Halothane decreased the amplitude and size of cortical excitatory post-synaptic potentials (EPSP) and also depressed CNS synaptic transmission either by reducing the output of transmitter from the presynaptic nerve terminal or by reducing the sensitivity of the post-synaptic membrane to the released transmitter substance (Richards, 1973).

Hepatic damage has been reported to occur following the use of halothane, however the incidence is extremely low. Repeated exposure to halothane apparently increases the likelihood of hepatocellular necrosis after halothane anesthesia and there is evidence that the reaction may be allergic in character (Klatskin, 1968). Ten-to-twenty percent of an administered dose of halothane is metabolized by the liver (Rehder et al, 1967) and some of the metabolic products have been shown to be hepatotoxic (Rosenberg & Wahlstrom, 1971). Nevertheless, the incidence of postanesthetic hepatitis is vanishingly small and a cause-and-effect relationship has not been clearly established (National Halothane Study, 1969).

DRUG INTERACTIONS

Drug interactions are considered to be the sequelae attending the simultaneous use of two or more drugs. The possibility that one drug may affect the activity of a concurrently administered agent has long been recognized, moreover, the continual expansion of the number of therapeutic agents available in clinical practice and the frequent use of multiple medications has led to an increased awareness of possible interactions between drugs. Two or more drugs administered at the same time or in close sequence may act independently of each other, or they may interact to increase or diminish the intended effect of one or both of the drugs, or new and unexpected reactions may occur. It has become clear that a major determinant in the development of toxic effects is the number of drugs administed during any period to a patient, with adverse reactions increasing proportionally to the number of drugs given and the duration of administration (Vere, 1965; Lasagna, 1965). Epidemiologic studies have demonstrated that the rate of adverse reactions to drugs increases from 4.2% when less than five drugs are given to 45% when twenty or more drugs are prescribed (Smith et al, 1966). Knowledge of possible drug interactions not only may prevent unexpected reactions, but also may lead to new therapeutic innovations.

The pharmacologic and toxic effects of any drug or its active metabolites is related to the free concentration of the active compound at its receptor sites. The concentration of drug available to the specific effector sites is influenced by the processes of absorption from the site of administration, distribution in in the blood and extravascular tissues, biotransformation and excretion. Thus, drug interactions may arise either from alterations in these parameters by another agent, or from a combination of their actions. Pharmacokinetic interactions are those that result in altered absorption, distribution or elimination of a drug. While pharmacodynamic interactions are those that involve the "biologic action" or effect of drugs, including enhanced toxicity of agents with similar adverse effects.

Clinical response to a medication can be altered by changing either the rate of drug absorption or the total quantity of drug absorbed, thereby significantly changing its concentration in the blood (Bederka et al, 1971; Saidman & Eger, 1973). A decrease rate of drug absorption secondary to the binding of one drug by another in the gastrointestinal (GI) tract, with formation of a poorly absorbed complex (e.g. tetracycline and multivalent metals), may result in an ineffective drug level at its receptor sites and delay the drug's onset of action. Other mechanisms for altering drug absorption include changes in gastric pH (altering passive non-ionic diffusion), use of oral resins (e.g. cholestyramine) and alterations in GI motility, as well as decreased blood flow to a parenteral depot.

During the transport and distribution of drugs via the blood, they may be reversibly bound to plasma or tissue proteins. Displacement of a drug from its secondary or "silent receptor" allows the drug to act at its biologic receptor and also facilitates its metabolism and excretion (e.g. phenylbutazone and coumarin). Receptor binding sites on cell membranes are involved in initiating a drug's biological response such that, agents which facilitate or antagonize the interaction of a drug with its receptor site will affect the drug's action.

It is well-known that one drug may either stimulate or inhibit the hepatic metabolism of another drug, and that the smooth endoplasmic reticulum ("microsomal fraction") is the primary site for biotransformation of drugs. Drugs can alter hepatic metabolism by stimulating or otherwise influencing microsomal enzymes and thereby, alter the intensity and duration of action of other drugs metabolized by the liver. Commonly used drugs (e.g. sedative-hypnotics) and a variety of agents present in the environment (e.g. insecticides) are capable of enhancing the activity of these enzymes. It would appear that compounds which are lipid soluble at physiologic pH, slowly metabolized by the liver, and strongly bound to plasma proteins (i.e. compounds not readily excreted by the kidney) are more likely to cause induction of hepatic drug-metabolizing enzymes. Inhibition of metabolism of one drug by another could be produced by irreversible inhibition of an enzyme responsible for the metabolism of the first drug (e.g. acetylcholine and organophosphates), or by competition as a substrate for the same drug-metabolizing enzyme (e.g. diphenylhydantion and isoniazid).

Drugs have been shown to alter the excretion of concurrently administered agents via a variety of mechanisms. Interactions affecting renal excretion will be clinically significant only when this is the primary route of elimination for the drug or its active metabolite(s) and alternative pathways are unable to compensate. Alterations in glomerular filtration, renal tubular reabsorption or secretion rate (e.g. probenecid and penicillin), as well as urinary pH, may influence drug clearance. Finally, alterations in the rate of biliary excretion of a drug might result from changes in bile flow or the rate of synthesis of proteins that function in the biliary conjugation-excretion mechanism (e.g. phenobarbital).

Pharmacodynamic interactions usually involve the effects of drugs with similar biologic actions (e.g. ethanol, barbiturates and benzodiazepines) or similar toxicities (e.g. aminoglycosides and ethacrynic acid). They also include interactions involving drug actions that are not immediately obvious from the major therapeutic effect of the agents (e.g. tricyclic antidepressants and guanethidine). Pharmacodynamic interactions also include drug-induced changes

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in electrolyte balance or other physiological variables that modify the action of another drug (i.e. diuretics and cardiac glycosides). Thus, drug interactions may arise through a direct effect of one compound upon another or indirectly by affecting another drug's absorption, transport, action at receptor binding sites, metabolism, or excretion.

Several other important variables to be considered in predicting the outcome of concurrent use of more than one drug include drug factors such as sequence, route and time of administration, duration of therapy, and dose and dosage form as well as patient factors (e.g. age, body temperature, renal and hepatic function, serum proteins and urinary pH as well as diet, environment, pharmacogenetic factors and disease state). It would appear that drug interactions are more frequently encountered with drugs which are lipid-soluble, bound to plasma proteins and slowly metabolized by the liver (e.g. coumarin).

Despite the ever increasing use of new and more potent drugs by the anesthesiologist, there is a paucity of data available in the literature regarding the interactions of drugs with the general anesthetic agents. Attempts have been made to evaluate the synergistic and antagonistic effects of premedicants, as well as other drugs, on general anesthetics (Dundee, 1958; Carson & Domino, 1962). The most commonly discussed drug-induced interactions in anesthesia include interactions between inhalational anesthetics and sedative-hypnotics (Kanto & Iisalo, 1973; Kanto & Pihlajamaki, 1973; Pearson et al, 1973; Vitez et al, 1973; Stoeltings et al, 1973; Lo & Cumming, 1975). Other well-known drug interactions in anesthesiology include those involving antihypertensive drugs (Dingle, 1966), antibiotics (Pittinger et al, 1958), narcotic analgesics (Cohen & Beecher, 1951), sympathominetic amines (Katz et al, 1962; Catenocci et al, 1963), and miscellaneous compounds such as gallamine (Walts &Priscott, 1965) and glucocorticoids(Lundy, 1953). Additionally, the effects on general anesthetic management of drugs known to alter CNS catecholamines has been investigated in our laboratories (Miller et al, 1968; Johnston et al, 1972, 1974, 1975a & 1975b) and elsewhere (Mueller et al, 1975).

In this thesis, an attempt has been made to study the various pharmacodynamic, as well as the pharmacokinetic, interactions between ketamine (a newer "fixed anesthetic" used for induction of anesthesia) and halothane (the most commonly used general anesthetic) using an animal model. Ketamine is frequently used clinically for the induction of anesthesia when conventional inhalational agents are to be used during surgery or as the sole anesthetic in cases of short duration (e.g. outpatient anesthesia). Clinically, we noted that many patients were lethargic for protracted periods post-operatively when ketamine was admnistered prior to, or concomitantly with, other general anesthetic agents. The duration of ketamine's effects had not been well-defined in previous studies and if prolonged effects were attributable to ketamine this might be a relative contraindication to its use for outpatient procedures. We have attempted to quantitate the magnitude and duration of ketamine's effect on halothane anesthesia and to determine if there is a relationship to ketamine per se or one of its metabolites. Following recovery from the anesthetic effects of ketamine, a residual amount of depression of the CNS might account for the lethargy noted clinically. Conversely, if a considerable analgesic effect is present at a time when lethargy is minimal, ketamine may have a distinctive advantage to supplement some anesthetic techniques.

Since the effects of induction agents on the potency of general anesthetics and the pharmacokinetics of these interactions have not been reported upon previously in the literature, a proposal was made to study; (1) the pharmacological actions of ketamine and its principal metabolite (i.e. hypnosis, analgesia and ataxia) as well as the effects of alterations in metabolism on

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those parameters, (2) the magnitude and duration of effect of ketamine and its major metabolite on halothane's anesthetic potency, (3) the effect of halothane anesthesia on ketamine's action as well as the mechanisms involved in altering ketamine's biodisposition. In our analysis of this drug-drug interaction, both the effects of ketamine on halothane's CNS activity as well as halothane's effects on ketamine were evaluated.

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CHAPTER II

PHARMACOLOGICAL PROPERTIES OF KETAMINE AND METABOLITE I

PHARMACOLOGICAL PROPERTIES OF KETAMINE AND METABOLITE I

To understand the nature and significance of ketamine's interactions with halothane anesthesia, it was necessary to assess the pharmacologic actions of ketamine (2-(o-chlorophenyl)-2-(methylamino)cyclohexanone) and its major metabolites, namely N-demethylated ketamine (also called metabolite I) and the cyclohexenone oxidation product of metabolite I (referred to as metabolite II). The proposed biotransformation pathway for ketamine (Chang & Glazko, 1974) is shown schematically in figure 2-1. The principal metabolites of ketamine in the rat, namely metabolites I and II (Chang et al, 1965; Chen, 1969), were also the major degradation products of ketamine recovered from human subjects (Chang, 1970). The relative cataleptic and anesthetic activities of metabolites I and II were reported to be only 1/10 and 1/100 those of the parent compound, respectively (Chen, 1969).

In clinical studies, ketamine has been reported to produce profound analgesia (Domino et al, 1965; Corssen & Domino, 1966; Virtue et al, 1967; Bovill & Dundee, 1971; Sadove et al, 1971; Bennett & Bullimore, 1973; Slogoff et al, 1974) and was purportedly more effective against pain involving the extremities and skeleton than against parietal or visceral pain (Corssen & Domino, 1966). In the only contolled study on ketamine analgesia, Bovill & Dundee (1971) reported that subhypnotic doses of ketamine caused a transient decrease in somatic pain and in contrast to the "antanalgesic" action of the barbiturates, analgesia was detected for prolonged periods of time following anesthetic doses. Other investigators have also commented on the duration of analgesia outlasting the period of anesthesia (Bjarnesen & Corssen, 1967; Aguado-Matorras et al, 1970).

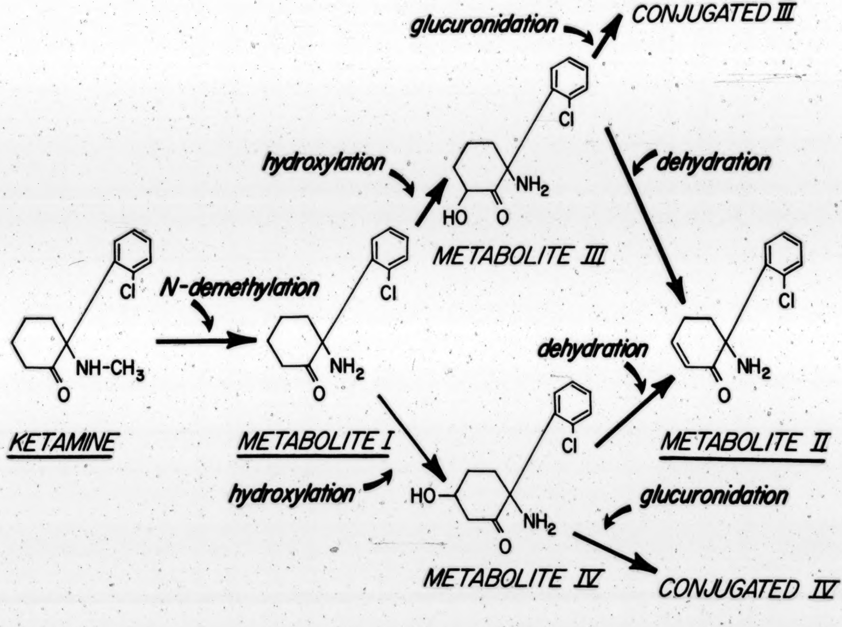

Figure 2-1. Proposed biotransformation pathway for ketamine, 2-(0-chlorophenyl)-2-(methylamino)cyclohexanone, modified from Chang & Glazko (1974).

In view of the paucity of controlled data available on ketamine analgesia and the difficulties inherent in the clinical assessment of pain and analgesia, we attempted to evaluate the analgetic properties of ketamine and its major metabolite using an animal model. The techniques used to assess analgesia included a method involving application of a mechanical pressure stimulus to the tail and a modification of the D'Amour and Smith (1941) rat "tail-flick" thermal method (Way et al, 1969). In addition, we sought to define two other pharmacologic properties of ketamine, namely hypnosis (i.e. loss of the righting reflex) and ataxia (i.e. abnormal gait) following both intramuscular (i.m.) and intravenous (i.v.) routes of administration.

Clinical use of ketamine may involve repetitive administration (Wilson et al, 1969b; Cronin et al, 1972; Bennett & Bullimore, 1973; Slogoff et al, 1974; Feingold & MacMahon, 1975; Amberg & Gordon, 1976), however the experimental data available regarding tolerance development is conflicting (Chen, 1969; Chang & Glazko, 1974; Marietta et al, 1974). We examined the effect of repeated injections of ketamine on the durations of the aforementioned pharmacologic responses following a challenge dose of the drug. Similar studies were carried out following pretreatment with either phenobarbital (a stimulator of hepatic smooth endoplasmic reticulum) or SKF 525A (an inhibitor of liver microsomal enzymes). These agents are known to modify the activity of the hepatic microsomal enzyme system and have been reported to influence both the *in vitro* hepatic metabolism and the plasma half-life of ketamine in rats (Cohen & Trevor, 1974).

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MATERIALS & METHODS

Intramuscular ketamine and metabolite I alone:

Male Sprague-Dawley rats (300-350 g) were divided into four groups and received either 5, 10, 20 or 50 mg/kg ketamine (Ketalar) intramuscularly in the hindlimb. The durations of (1) hypnosis or loss of the righting reflex, (2) analgesia or altered responsiveness to a painful mechanical tail-clip stimulus, and (3) ataxia or abnormal gait were assessed in each animal. Similar groups of rats received i.m. metabolite I 20, 50 or 100 mg/kg (dissolved in 0.1N HCl and diluted to the appropriate concentration with saline). The same pharmacologic effects were evaluated after metabolite I administration.

Pretreatment followed by intramuscular ketamine challenge:

In a second study, younger (130-150g) male S-D rats were pretreated with phenobarbital (35 mg/kg IP twice daily for three days), 2-diethylamino-ethyl-2,2-diphenylvalerate HCl (SKF 525A 25 mg/kg IP) or ketamine (Ketalar 50 mg/kg IP twice daily for three days). Final phenobarbital and ketamine injections were administered twenty-four hours prior to the challenge ketamine dose, while the SKF 525A injection was made one hour before the ensuing experimentation. Control rats were administered equal volumes of normal saline twice daily for three days and one hour prior to the ketamine challenge dose. All animals received the same total number of pretreatment injections. Following pretreatment, intramuscular ketamine 50 mg/kg was administered into the hindlimb and the durations of hypnosis, analgesia and ataxia were measured in all animals as described above.

Comparison of analgesic properties of i.v. ketamine and thiopental:

In a third study, a group of smaller S-D rats (110-130 g) was administered doses of either ketamine (5, 10, 20, 30 or 50 mg/kg) or metabolite I (20, 40, 60 or 80 mg/kg) intravenously via the caudal vein. It was necessary to use smaller rats in order to facilitate the i.v. injections. The duration of analgesia was assessed by means of the tail-flick method of D'Amour and Smith (1941). A mean baseline response (1.0 ± 0.2 units) to tail thermal stimulation was established for each animal preceding intravenous ketamine. Tail-flick response then was measured at the time the animal recovered its righting reflex and at subsequent four-minute intervals. Analgesia was judged to have ceased when the tail response time returned to within 0.2 units of the baseline. The duration of hypnosis also was determined as described previously.

A similar group of rats were injected intravenously with various doses of thiopental (6.25, 12.5, 25 or 50 mg/kg) and the durations of analgesia and hypnosis were determined in an analogous fashion.

Pretreatment followed by i.v. ketamine challenge:

In a fourth study, male S-D rats (100-120 g) were pretreated with either phenobarbital (35 mg/kg IP b.i.d. for 3 days), SKF 525A (25 mg/kg IP), ketamine (40 mg/kg IP b.i.d. for 3 days), or saline prior to a 30mg/kg i.v. ketamine challenge. Animals pretreated with phenobarbital or ketamine received their final injection eighteen hours prior to the ketamine challenge, while the SKF 525A group was injected one hour prior to the challenge. The durations of hypnosis, analgesia (using the thermal stimulus method), and ataxia were measured as described above.

Statistical methods:

The mean and standard error (S. E.) of each variable, for every group of rats, was calculated. Means were compared by paired and unpaired Student's t-tests and differences with a $P < 0.05$ were considered significant. The log dose-response curves for analgesia following i. v. ketamine or metabolite I administration were obtained by linear regression analysis using the method of least squares.

Chemicals:

All reagents were obtained from available commerical sources. Ketamine and metabolite I were obtained from Parke, Davis & Company (Detroit, Mich) and SKF 525A was obtained from Smith, Kline and French Laboratories (Philadelphia, Pa).

RESULTS

The durations of analgesia, as well as hypnosis and ataxia, following intramuscular administration of ketamine or its principal metabolite in the first group of rats are summarized in table 2-1. Only the 50 mg/kg dose of ketamine gave significant hypnosis while analgesia and ataxia followed all doses of ketamine and metabolite I, the duration of each pharmacologic effect being related to dose. The ketamine/metabolite I potency ratio was estimated to be 4:1. At the lower doses, it was noted that the onset of analgesia was not as rapid as the onset of hypnosis after ketamine administration.

The log-dose response curves for the duration of analgesia following intravenous doses of ketamine or metabolite I are shown in figure 2-2. The parallelism of the log-dose response curves for ketamine and metabolite I suggests a similar mechanism of action for both in producing analgesia. As expected, ketamine was again found to be more potent than metabolite I with respect to its pharmacologic actions. The analgesia produced following intravenous administration of thiopental was evaluated in an analogous manner. However, in the thiopental group the duration of hypnosis actually exceeded the duration of analgesia at all doses tested (unreported data).

The effects of drug pretreatment on acute pharmacological responses to an intravenous injection of ketamine (table 2-3) were similar in most respects to those seen following an intramuscular challenge dose (table 2-2). None of the pretreatment schedules resulted in a significant effect on the duration of ketamine-induced hypnosis. The duration of ataxia was reduced an average of 35% and 49% by phenobarbital and ketamine pretreatment, respectively, and

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TABLE 2-1

Pharmacological Effects Following Admininstration of Ketamine or Metabolite I in the Rat

Various doses of either ketamine or metabolite I were injected intramuscularly into the right hamstrings area and the durations of hypnosis, analgesia and ataxia were measured as described under "Materials & Methods." Values represent means ± S. E. M. of twelve animals.

	Dose (mg/kg)	Number of Animals	Hypnosis (min.)	Analgesia (min.)	Ataxia (min.)
Ketamine	5	12	0	2 ± 1	8 ± 1
	10	12	0	10 ± 2	21 ± 1
	20	12	1 ± 1	28 ± 5	38 ± 2
	50	12	9 ± 2	54 ± 7	72 ± 5
Metabolite I	20	12	0	5 ± 3	10 ± 3
	50	12	0	9 ± 3	29 ± 3
	100	12	1 ± 1	26 ± 7	69 ± 9

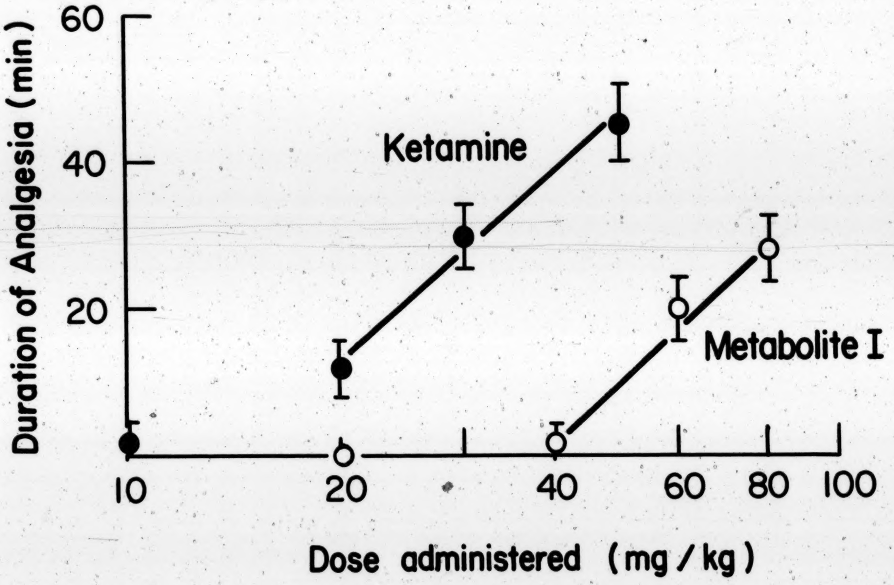

Figure 2-2. Dose-response curves for the duration of analgesia as a logarithmic function of the dose of intravenous ketamine or metabolite I. Values are means of five animals at each dose and vertical bars represent ± S. E. M.

TABLE 2-2

Effects of Drug Pretreatment on Acute Pharmacological Responses to an I.M. Ketamine Challenge in the Rat

The animals were pretreated with either saline, phenobarbital, SKF 525A or ketamine and the durations of hypnosis, analgesia and ataxia were measured following a 50 mg/kg i.m. ketamine challenge dose as described under "Materials & Methods." Values represent means ± S.E.M. for fifteen animals.

Pretreatment regimen	Number of animals	Hypnosis min. / % Δ		Analgesia min. / % Δ		Ataxia min. / % Δ	
Control group:							
Saline	15	11 ± 1		31 ± 3		57 ± 3	
Experimental group:							
Phenobarbital	15	11 ± 1	0	29 ± 3	-7%	37 ± 2	-35%*
SKF 525A	15	12 ± 1	+11%	34 ± 4	+10%	103 ± 5	+81%*
Ketamine	15	10 ± 1	- 9%	19 ± 2	-39%*	28 ± 2	-51%*

* Significantly different from controls, $P < 0.05$ by unpaired Student's t-test

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TABLE 2-3

Effects of Drug Pretreatment on Acute Pharmacological Responses to an I. V. Ketamine Challenge in the Rat

The animals were pretreated with either saline, phenobarbital, SKF 525A or ketamine and the durations of hypnosis, analgesia and ataxia were measured following a 30 mg/kg i. v. ketamine challenge dose as described under "Methods & Materials." Values represent means ± S. E. M. for eleven animals.

Pretreatment regimen	Number of animals	Hypnosis min. / % Δ		Analgesia min. / % Δ		Ataxia min. / % Δ	
Control group:							
Saline	11	7 ± 1		29 ± 3		36 ± 2	
Experimental groups:							
Phenobarbital	11	7 ± 1	0	16 ± 3	-45%*	23 ± 2	-36%*
SKF 525A	11	8 ± 1	+14%	59 ± 5	+103%*	68 ± 5	+89%*
Ketamine	11	6 ± 1	-14%	13 ± 3	-55%*	19 ± 2	-47%*

* Significantly different from controls, $P < 0.05$ by unpaired Student's t-test.

prolonged an average of 85% by SKF 525A pretreatment. The duration of analgesia was influenced in a similar fashion following the intravenous ketamine challenge dose; however, only the ketamine pretreated group produced a significant alteration in the duration of analgesia following the intramuscular challenge. Ketamine pretreatment was found to produce larger decreases in the durations of analgesia and ataxia than did phenobarbital pretreatment.

DISCUSSION

The dose-related pharmacologic actions of ketamine and its principal metabolite, metabolite I, following parenteral administration included hypnosis, analgesia and ataxia. The parent compound and its N-demethylated metabolite appear to possess identical pharmacologic properties with a similar mechanism of action. Ketamine appeared to be three-to-five times more potent based on doses required for a "threshold response" and on a comparison of the durations of action. Post-hypnotic analgesia following ketamine administration appeared to be a specific property of the drug as i.v. administration of hypnotic doses of thiopental caused no post-hypnotic analgesia. Furthermore, ataxia was considered to be of central origin since the levels of ketamine and metabolite I that occurred in skeletal muscle *in vivo* had no effect on *in vitro* neuromuscular transmission as assessed using the Bulbring (1946) isolated rat phrenic nerve diaphragm preparation (unreported data).

In an effort to further elucidate the mechanism(s) terminating the pharmacologic effects of ketamine, animals were pretreated with ketamine as well as agents anticipated to modify hepatic microsomal metabolism (e.g. phenobarbital and SKF 525A). A previous study from our laboratories (Cohen & Trevor, 1974) demonstrated that the duration of post-hypnotic ataxia caused by intravenous administration of ketamine to rats was shortened by pretreatment with phenobarbital or ketamine and prolonged by pretreatment with SKF 525A. Additionally, phenobarbital pretreatment was shown to stimulate while SKF 525A inhibited the *in vitro* hepatic metabolism of ketamine.

The pretreatment schedules employed in these studies did not effect the duration of ketamine-induced hypnosis, suggesting that the termination of this action is unrelated to the rate of metabolic inactivation of the drug. These results are consistent with the hypothesis that the duration of ketamine-induced hypnosis is primarily related to the rate of redistribution of the highly lipophilic drug (Cohen & Trevor, 1974). Moreover, ataxia was influenced by the pretreatment regimes in an identical manner to that reported previously, implying that the rate of hepatic metabolism of ketamine influences the duration of this post-hypnotic event.

The absence of a significant effect on analgesia following alterations in ketamine's metabolism in the group receiving an intramuscular ketamine challenge, in contrast to the effects seen following the intravenous challenge, might reflect the fact that the technique employing mechanical pressure as a stimulus for pain is less sensitive than the thermal technique. Furthermore, since the duration of analgesia is intermediate in time between hypnosis and ataxia, one might predict that the duration of analgesia would be determined by a combination of both redistributional and metabolic events. This may also be a partial explanation for the fact that only the ketamine pretreated group demonstrated a significant change in the duration of post-hypnotic analgesia after i.m. ketamine. Although the duration of analgesia was altered in a manner more analogous to ataxia following the i.v. ketamine challenge, the magnitude of the changes produced were reduced in the phenobarbital groups relative to the ketamine-pretreated animals. This finding was unexpected because phenobarbital pretreatment was more effective than ketamine pretreatment in stimulating in vitro liver metabolism of ketamine using the identical pretreatment schedule (Marietta et al, 1974). These data suggest that repetitive administration of ketamine may produce "tolerance" to the analgetic actions of the drug by a mechanism(s) involving not only enhanced hepatic metabolic inactivation, but also functional or "pharmacodynamic" tolerance. These

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studies raise the possibility that in the clinical use of ketamine, the duration of certain of the pharmacological effects of the drug may be affected by prior administration of agents (including ketamine itself) that can influence liver microsomal enzyme systems involved in drug metabolism.

SUMMARY

Ketamine's pharmacologic actions included hypnosis, analgesia and ataxia following both i.m. and i.v. injection, with the duration of each event being related to dose. Although it was less potent, metabolite I possessed pharmacological properties which were similar to those of the parent compound and probably involves the same mechanism(s) of action as ketamine in its effects on the CNS. The ketamine/metabolite I potency ratio was estimated to be roughly 4:1 . Analgesia was a specific post-hypnotic property of these compounds in contrast to other commonly used induction agents (e.g. thiopental).

The duration of ketamine-induced hypnosis was not significantly affected by alterations in ketamine's metabolism. On the other hand, the durations of ataxia and to a lesser extent analgesia, were reduced following enhancement of ketamine's metabolism with phenobarbital pretreatment and prolonged by inhibiting ketamine's metabolism with SKF 525A. Pretreatment with ketamine itself resulted in alterations of ketamine's post-hypnotic actions which were similar to those seen with phenobarbital. Moreover, the effects of ketamine pretreatment on post-hypnotic events were of greater magnitude than could be accounted for solely on the basis of its self-inductive effects on metabolism. This was especially apparent with respect to analgesia, where both distributional and redistributional events as well as metabolism seem to play important roles. These studies suggest that repeated use of ketamine also may lead to the development of pharmacodynamic "tolerance" to its post-hypnotic CNS actions.

CHAPTER III

EFFECTS OF KETAMINE ON HALOTHANE ANESTHESIA

EFFECTS OF KETAMINE ON HALOTHANE ANESTHESIA

Ketamine was introduced as a rapid, short-acting parenterally administered anesthetic. In conflict with the suggestion of its short action, several investigators in West Germany have noted a prolonged recovery period. Studies by Nagel (1969) on optico-kinetic and sight line nystagmus as well as rotatory stimulus threshold of the vestibular apparatus, Doenicke (1969) on minimization of the psycho-physic abilities, Kreuscher (1969) on sensomotoric reaction, motoric coordination and alertness, ability to concentrate, comprehend and recall, Westhues (1969) on the recovery time of pain-response, accessibility and orientation to person, place and time, and Stocker (1969) on EEG changes following ketamine administration, all indicate that ketamine may not be as "short-acting" as was initially thought. Furthermore, Eckart (1969) reported that when ketamine was used as an induction agent combined with nitrous oxide, halothane, oxygen and muscle relaxants, the recovery period appeared to be markedly prolonged. It was not known whether protracted recovery following ketamine administration was related to concomitant use of other drugs (Kanto & Pihlajamaki, 1973; Kanto & Iisalo, 1973; Pearson et al, 1973), formation of active ketamine metabolite(s), or persistence of ketamine itself.

Since no study has demonstrated the time course of the action of ketamine given in the presence of conventional inhalation anesthetics on the central nervous system, we sought to define the anesthetic properties of ketamine in the presence of halothane anesthesia by measuring its effect(s) on the minimum alveolar concentration (MAC) of halothane. MAC has been defined as the lowest alveolar anesthetic concentration that produces immobility in 50% of those animals or patients exposed to a noxious stimulus (Eger et al, 1965).

It is an ED50 of anesthesia and a measure of anesthetic potency.

We also determined alterations in the halothane anesthetic requirement following administration of the principal metabolite of ketamine, namely metabolite I. By measuring brain and plasma levels of ketamine and metabolites I and II, we were able to examine the relationships between drug levels and effects on halothane MAC.

MATERIALS & METHODS

Male Sprague-Dawley rats, weighing 300-350 g, were used in the following four experiments. One experimental group received ketamine alone while a second group received metabolite I only. The remaining two groups received the same doses of ketamine or metabolite I during halothane anesthesia.

Ketamine alone:

Rats in each of four dosage groups received 5, 10, 20 or 50 mg/kg of ketamine (Ketalar) intramuscularly in the hindlimb. One, two, three, and four hours after each dose of ketamine, four rats were rapidly anesthetized with 100% cyclopropane and blood was obtained by direct cardiac puncture. The blood was heparinized and centrifuged for ten minutes to obtain plasma, which later was analyzed for ketamine and its major metabolites. After cardiac puncture, the animals were decapitated. The cerebral hemispheres were transferred to ice and the superficial blood vessels removed. One part brain tissue was added to nine parts physiologic saline solution, homogenized, and centrifuged at 100,000 x g for sixty minutes. The supernatant was analyzed for ketamine, metabolite I, and metabolite II as described below.

Metabolite I alone:

Groups of rats received , intramuscularly, 20, 50 or 100 mg/kg metabolite I. Three animals in each group were sacrificed at one-hour intervals and plasma and brain samples were obtained and analyzed for metabolites I and II as noted below.

Ketamine-halothane:

Four groups of five rats were anesthetized with halothane, tracheostomies performed, and anesthetic requirement (i.e. MAC) determined as described in the appendix. Assuming sufficient time is allowed for equilibration, the partial pressure of halothane in alveolar gas or arterial blood closely approximates the halothane tension at its site of action in the CNS. Five, 10, 20, or 50 mg/kg of ketamine then were administered intramuscularly (one dose for each group of five rats) and MAC redetermined 1-2 hours (MAC 1-2), 3-4 hours (MAC 3-4), and 5-6 hours (MAC 5-6) after injection. These animals were sacrificed six hours after the ketamine injection.

Additionally, four groups of rats similarly were anesthetized with halothane, tracheostomized, and end-tidal halothane concentrations were maintained at MAC as determined above. Ketamine 5, 10, 20, or 50 mg/kg i.m., was administered (one dose to each group of rats) following which halothane concentrations were reduced parallel to the reductions determined previously in animals in which MAC values had been measured following identical doses. In each group, five animals were sacrificed at hourly intervals for four hours after ketamine administration. Plasma and brain extract samples were obtained for ketamine, metabolite I and metabolite II analyses as described below. The plasma and brain levels of metabolite I following i.m. injection of ketamine were measured and the magnitudes of depression attributable to these levels of metabolite I determined from the percentage decreases in MAC 1-2 values after i.m. administration of metabolite I. This depression in halothane anesthetic requirement resulting from the formation of metabolite I from ketamine then was subtracted from the measured depressions in MAC 1-2 following ketamine administration to ascertain the effects due to ketamine itself.

Rectal temperatures were maintained at 37 ± 1° C with a heating pad.

End-tidal or "alveolar" gas samples were analyzed for halothane and carbon dioxide using Beckman infrared analyzers.

Metabolite I-halothane:

Three groups of rats were prepared as in the ketamine-halothane study except that each group received 20, 50 or 100 mg/kg i.m. of metabolite I. At each dose, MAC changes were determined in five animals while the remaining rats were maintained at comparable halothane levels. As in the previous study, equal numbers of the remaining rats were sacrificed at one, two, three and four hours after injection of metabolite I. Plasma and brain extract samples were obtained as described above for analyses of metabolites I and II.

Assay for ketamine and its metabolites:

Early analytical studies on ketamine were based on the use of the methyl orange procedure for assay of organic bases (Brodie et al, 1947). The method lacked both specificity and sensitivity and was replaced by a fluorescent dye procedure (Dill et al, 1971). In an effort to improve the analytical sensitivity, a gas-liquid chromatographic (GLC) procedure for ketamine estimation in plasma was developed (Chang & Glazko, 1972). The procedure was based upon heptafluorobutyryl derivatization and utilization of an electron-capture detector. It proved to be highly sensitive and specific for ketamine and metabolites I and II. This procedure has been adapted for the estimation of tissue levels of ketamine and its metabolites.

Extraction procedure for ketamine and its metabolites:

Samples of plasma and supernatant from homogenized tissues were pipetted into glass stoppered conical centrifuge tubes (15x135 mm) with additional deionized water and 0.1N HCl added to obtain a final volume of 2 ml and a final acidity of 0.5N HCl. The internal standard (2-amino-2-(o-bromophenyl)-2-(methylamino)cyclohexanone) was added to a final concentration of 0.25 μg/ml and the tubes were agitated on a vortex mixer. After addition of 0.1 ml of a 10% borax buffer and 5 ml of analytical-grade benzene, the tubes were hand shaken for sixty seconds and subsequently centrifuged at 1,750 rpm for thirty minutes. The benzene layer containing the extracted drug and metabolites was transferred to a clean glass-stoppered conical centrifuge tube for derivatization. Heptafluorobutyric anhydride (0.1 ml) and KOH-dried pyridine (0.1 ml) were added and thoroughly mixed on a vortex mixer. The mixture was allowed to stand at room temperature for sixty minutes, with agitation every ten minutes. The benzene layer then was shaken for five minutes with 2 ml of 0.5 N NaOH to remove excess reagent. The aqueous phase (bottom) was removed, 2 ml of 0.25N HCl added, and the resulting mixture shaken for five minutes. After centrifugation for fifteen minutes at 1,750 rpm, the lower aqueous phase was discarded. Anhydrous sodium sulfate (1 g) was added to the remaining benzene layer, and the tubes were stoppered and agitated on a vortex mixer. Finally, 0.5-2.0 μl of the benzene solution was injected into the GLC column using a microliter syringe for analysis of ketamine and metabolites I and II.

Analysis of ketamine and its metabolites:

Plasma and tissue levels of ketamine and its two principal metabolites were assayed on a Varian 1200 aerograph GLC with an electron-capture detector (tritium foil) using a modified version of the Chang and Glazko procedure (1972). The carrier gas was 95% argon/5% methane at a flow rate of 20 ml/min. The column (3 mm I.D.) was packed with 3% OV-17 Gas Chrom Q (100/120 mesh). The column temperature was maintained at 192° C with the flash heater at 220° C and the detector at 225° C. A representative GLC record demonstrating the separation pattern of ketamine, metabolite I and metabolite II extracted from rat brain tissue following ketamine 50 mg/kg i.m. is shown in figure 3-1. Standard curves based on peak height ratios of standards to internal standard were linear from 0.01 to 1.0 µg for ketamine and metabolite II and from 0.002 to 0.5 µg for metabolite I. Duplicate assays demonstrated good reproducibility with a variation of ±3%, and standard curves were prepared for each series of analyses. When the drug or its metabolites were added to plasma or various tissue homogenates, the analytical recoveries ranged from 96-100%.

Statistical methods:

The mean and S. E. for each group at every time interval were calculated and compared by unpaired analyses using the Student's t-test. The plasma and brain levels of ketamine and its two principal metabolites were plotted against time on semilogarithmic paper and a linear regression obtained by the method of least squares. The relationship between drug levels in the plasma or brain and the effect on halothane MAC also were described with linear regression analyses.

Chemicals:

All reagents were obtained from available commerical sources. Ketamine hydrochloride (Ketalar), metabolite I, metabolite II and the internal standard were gifts from Parke, Davis & Co. (Detroit, Michigan). Halothane (Fluothane) was generously provided by Ayerst Laboratories Inc. (New York, NY).

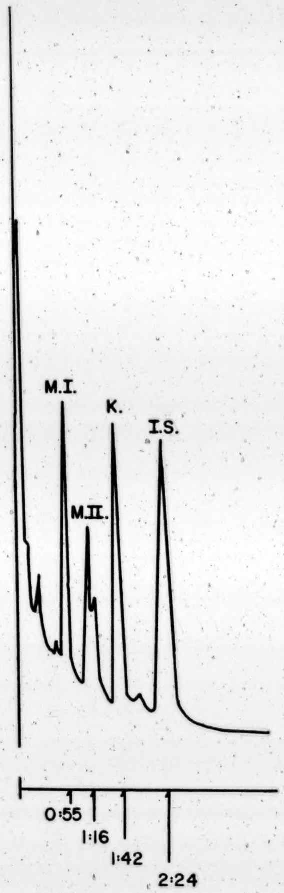

Figure 3-1. Representative gas-liquid chromatogram of metabolite I (M. I.), metabolite II (M. II.), ketamine (K.) and internal standard (I. S.) following extraction from rat brain tissue. Retention times (minutes : seconds) are indicated under the respective peaks.

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RESULTS

In spite of the fact that only the highest dose of ketamine used in this study gave significant hypnosis when administered alone (table 2-1), all doses of ketamine and metabolite I depressed halothane MAC (table 3-1, figs. 3-2 to 3-5). Although MAC returned towards control levels with time, significant depression remained 5-6 hours after injection of 50 mg/kg ketamine or 100 mg/kg metabolite I. Correlation coefficients of 0.966 and 0.938 were ascertained by linear regression analyses of the depression in halothane MAC 1-2 as a logarithmic function of the doses of ketamine and metabolite I, respectively (fig. 3-2). The log dose-response curves for ketamine and metabolite I were essentially parallel (slopes of -0.055 and -0.048 ΔMAC/mg drug(log) /kg body weight, respectively) and suggested a potency ratio for ketamine : metabolite I of approximately 3:1. A similar relationship was maintained at 3-4 hours after ketamine injection (fig. 3-3).

Brain ketamine concentrations (fig. 3-7) were approximately four times those in plasma (fig. 3-6) in both halothane anesthetized and unanesthetized rats at one-to-four hours following i.m. ketamine, which is similar to the ratio reported by Cohen et al (1973). Halothane altered the pharmacokinetic properties of ketamine such that the levels tended to be higher at the initial time period studied with a concomitant reduction in the slope of the decay curves. Metabolite I plasma and brain decay curves (figs. 3-8 & 3-9) following i.m. ketamine also demonstrated a decreased slope under halothane anesthesia. The brain to plasma metabolite I ratios were significantly lower than those for ketamine, consistent with the decreased lipid solubility of the N-demethylated metabolite (Cohen & Trevor, 1974).

TABLE 3-1

Halothane MAC Values Following I.M. Ketamine or Metabolite I in the Rat

Actual halothane MAC values before and one-to-two hours after various doses of ketamine or metabolite I as described under "Materials & Methods." Values represent means ± S.E.M. for five animals.

	Dose (mg/kg)	Number of Animals	Control MAC (% halothane)	MAC 1-2 (% halothane)	% Decrease in MAC
Ketamine	5	5	0.99 ± 0.05	0.82 ± 0.03	16%
	10	5	1.04 ± 0.05	0.73 ± 0.05	30%
	20	5	1.10 ± 0.03	0.66 ± 0.02	40%
	50	5	1.09 ± 0.04	0.48 ± 0.01	56%
Metabolite I	20	5	1.14 ± 0.05	0.89 ± 0.04	21%
	50	5	1.07 ± 0.02	0.71 ± 0.02	34%
	100	5	1.03 ± 0.03	0.50 ± 0.04	51%

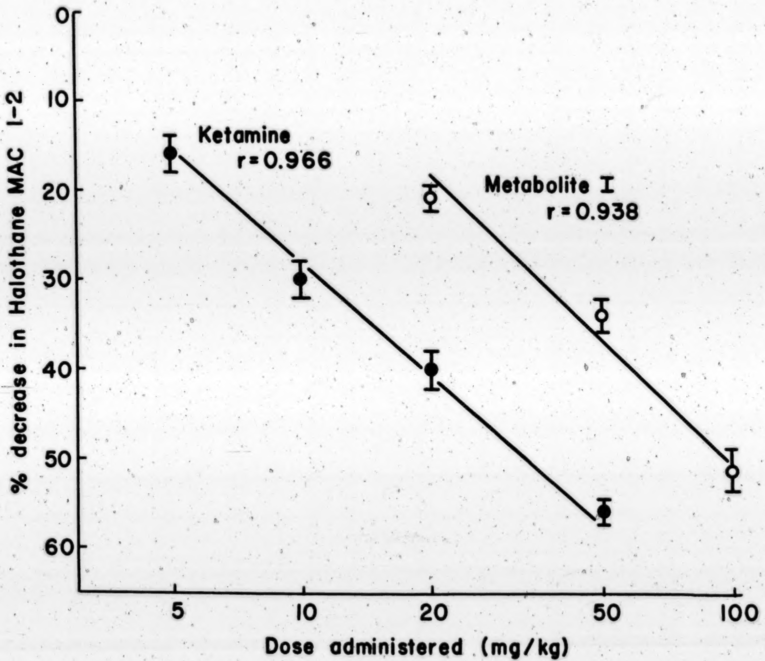

Figure 3-2. Log-dose response curves for the effect of ketamine or metabolite I on halothane MAC 1-2. The correlation coefficients (r-values) for ketamine and metabolite I are shown. Values represent the mean depression in halothane MAC at 1-2 hours after an i.m. injection for five animals and the vertical bars are ± S.E.M.

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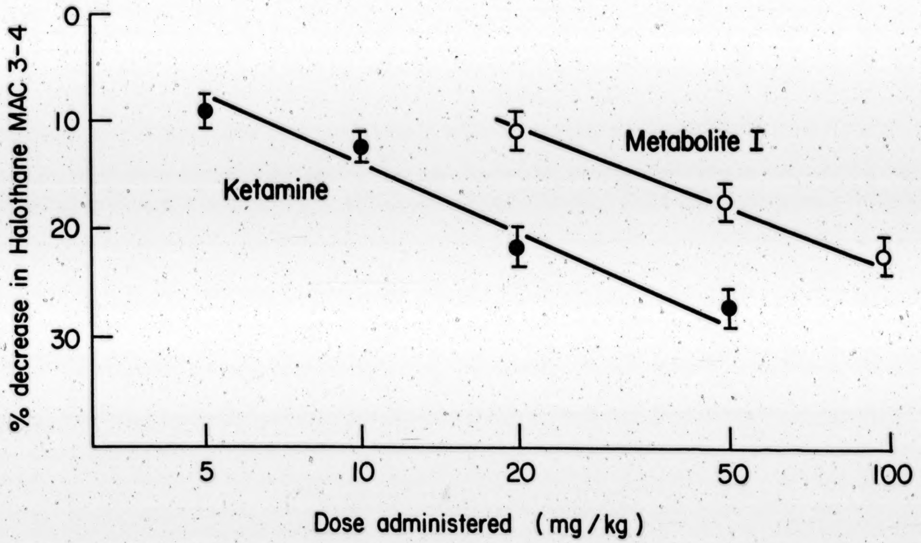

Figure 3-3. Log-dose response curves for the effect of ketamine or metabolite I on halothane MAC 3-4. Values represent the mean depressions in halothane MAC at 3-4 hours following an i.m. injection for five animals. The vertical bars are ± S.E.M.

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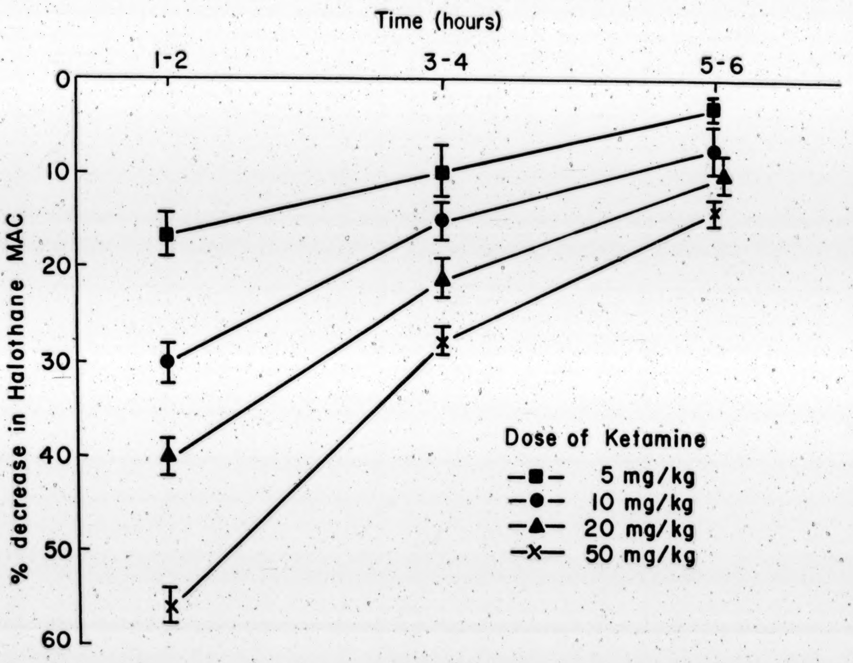

Figure 3-4. Changes in halothane MAC at various time intervals after i.m. injection of ketamine. Values are means of five animals and vertical bars represent ± S. E. M.

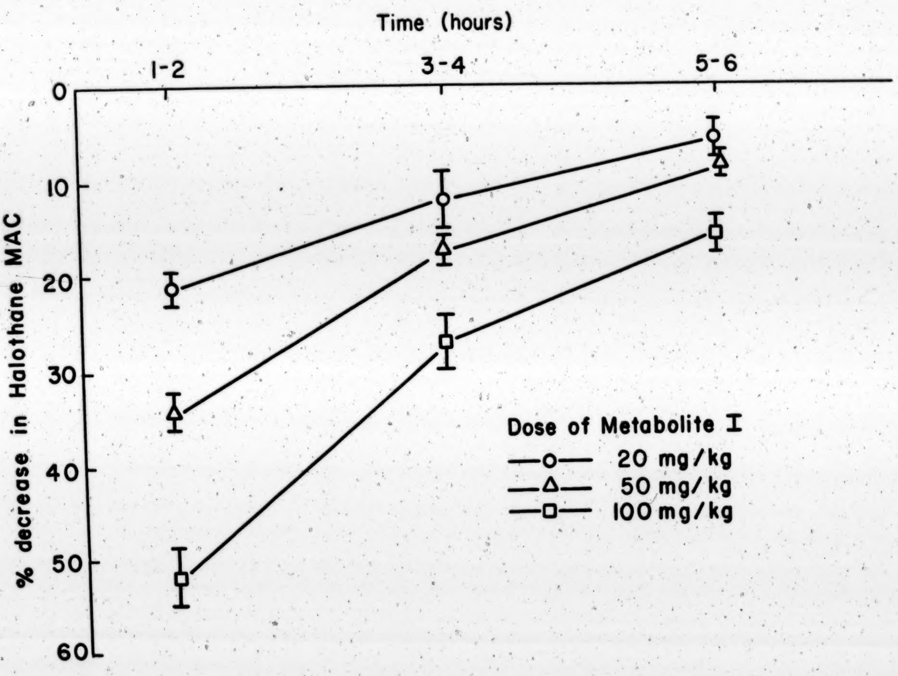

Figure 3-5. Changes in halothane MAC at various time intervals after i.m. injection of metabolite I. Values are means of five animals and vertical bars represent ± S.E.M.

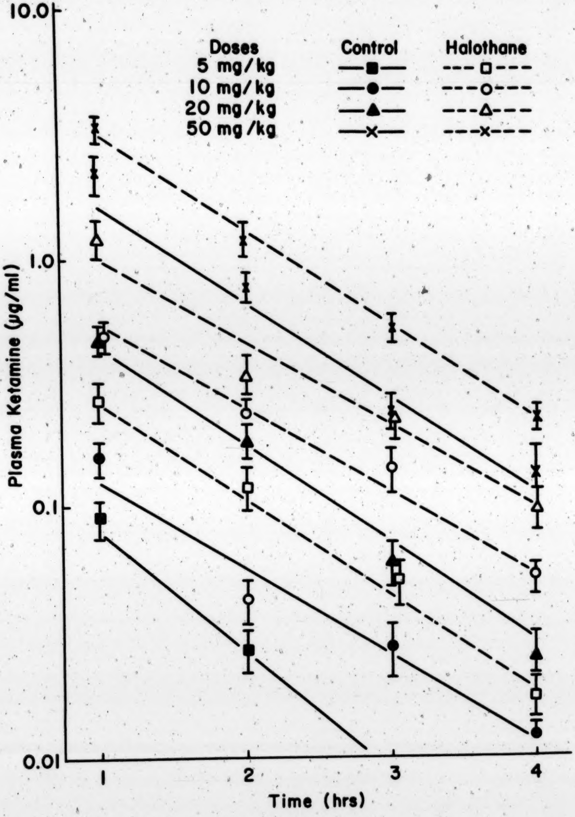

Figure 3-6. Changes in plasma levels of ketamine with time in unanesthetized (control) and anesthetized (halothane) animals following i.m. injection of ketamine. Values are means of four animals and vertical bars represent ± S. E. M.

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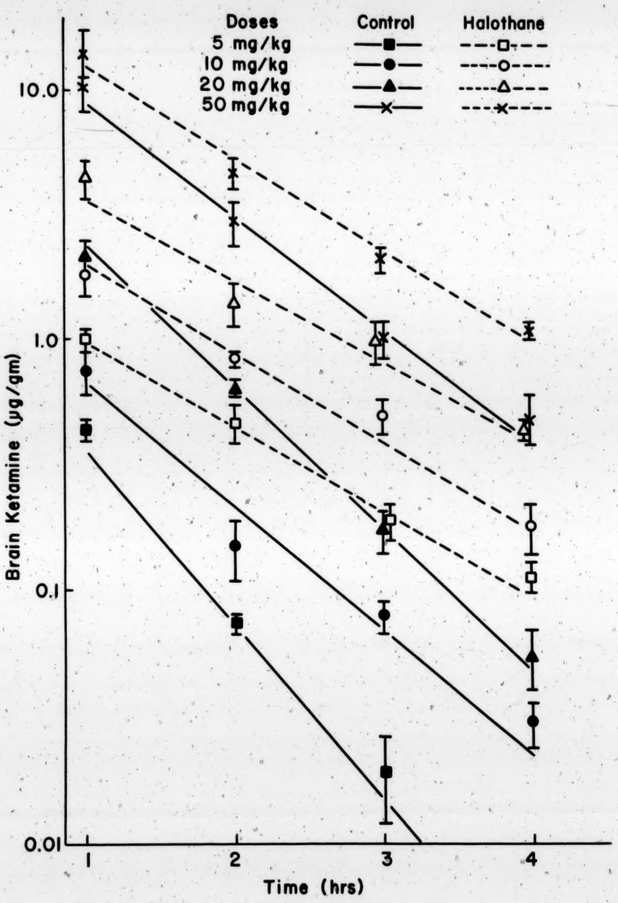

Figure 3-7. Changes in brain levels of ketamine with time in unanesthetized (control) and anesthetized (halothane) animals following i.m. injection of various doses of ketamine. Values are means of four animals and vertical bars represent ± S. E. M.

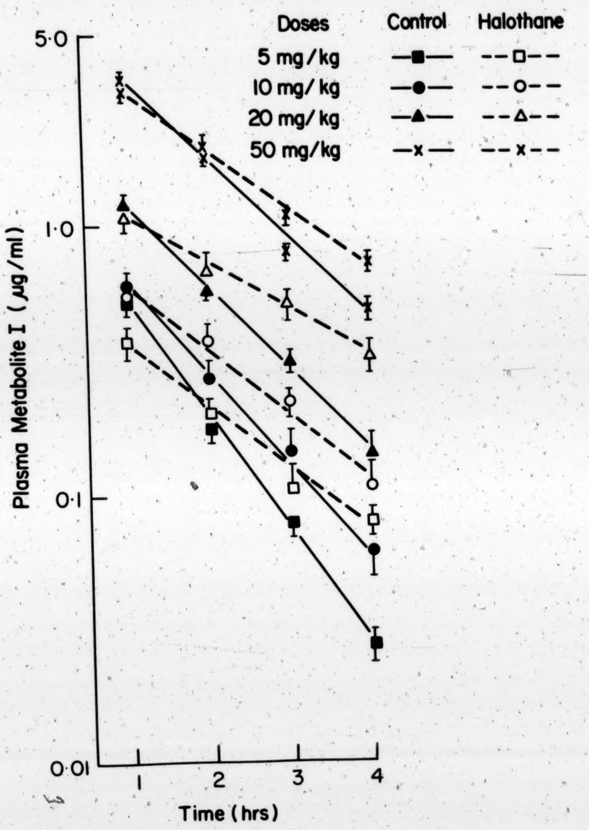

Figure 3-8. Changes in plasma levels of metabolite I with time in unanesthetized (control) and anesthetized (halothane) animals following i.m. injection of various doses of ketamine. Values are means of four animals and vertical bars represent ± S.E.M.

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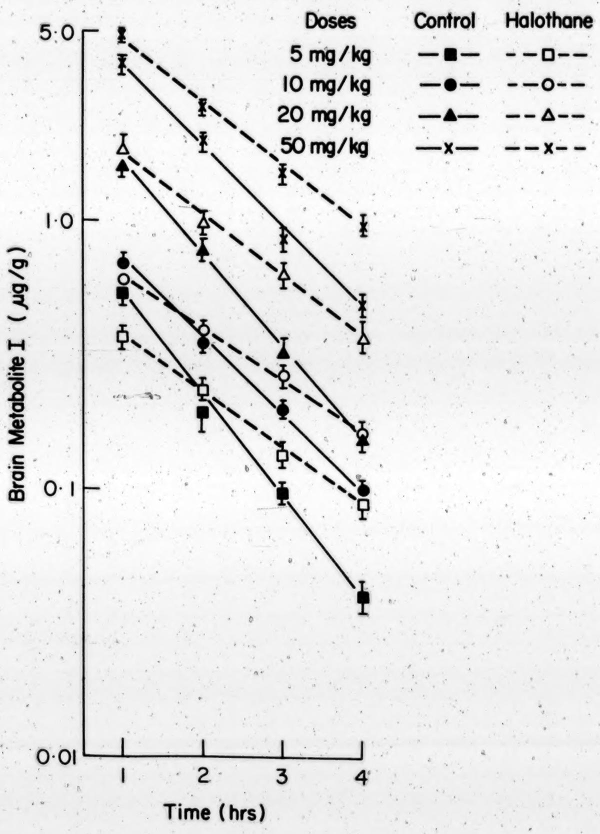

Figure 3-9. Changes in brain levels of metabolite I with time in unanesthetized (control) and anesthetized (halothane) animals following i.m. injection of various doses of ketamine. Values are means of four animals and vertical bars represent ± S.E.M.

Ketamine and metabolite I in the plasma correlated with reductions in halothane MAC 1-2 (fig. 3-10). Similarly, brain levels of ketamine and metabolite I correlated with MAC 1-2 (fig. 3-11). The amount of metabolite I formed accounted for about 20-25% of the measured decrease in halothane MAC 1-2 following i.m. injection of ketamine. For example, MAC 1-2 was found to be decreased by 40% following administration of ketamine, 20 mg/kg, i.m. (table 3-1). By extrapolation, the amount of metabolite I measured in the plasma (0.98 ± 0.21 µg/ml) would have resulted in about a 10% reduction in MAC 1-2 (fig. 3-10). Thus, the percentage depression in MAC 1-2 corresponding to plasma ketamine alone was estimated to be 30% (fig. 3-10). Similarly, the amount of metabolite I found in the brain (1.33 ± 0.17 µg/g) would have accounted for a 7% reduction in MAC 1-2 (fig. 3-11). The percentage decrease in MAC 1-2 due to ketamine alone would be 33% (fig. 3-11). Hence, for this particular dose of ketamine, metabolite I levels in the plasma and brain would account for 25% and 18%, respectively, of the total decrease in halothane MAC 1-2.

Significant plasma levels of metabolite II were detected after all doses of ketamine when administered in the presence of halothane (table 3-2); however, in the control groups detectable amounts of metabolite II were noted only after the 20 and 50 mg/kg doses of ketamine. Metabolite II was detected in the brain following i.m. injection of metabolite I, and there was a non-significant decrease in the slope of the brain and plasma decay curves for metabolites I and II when metabolite I was administered intramuscularly under halothane anesthesia (unreported data). In addition, there were no correlations between the decreases in halothane MAC and levels of metabolite II following either ketamine or metabolite I administration.

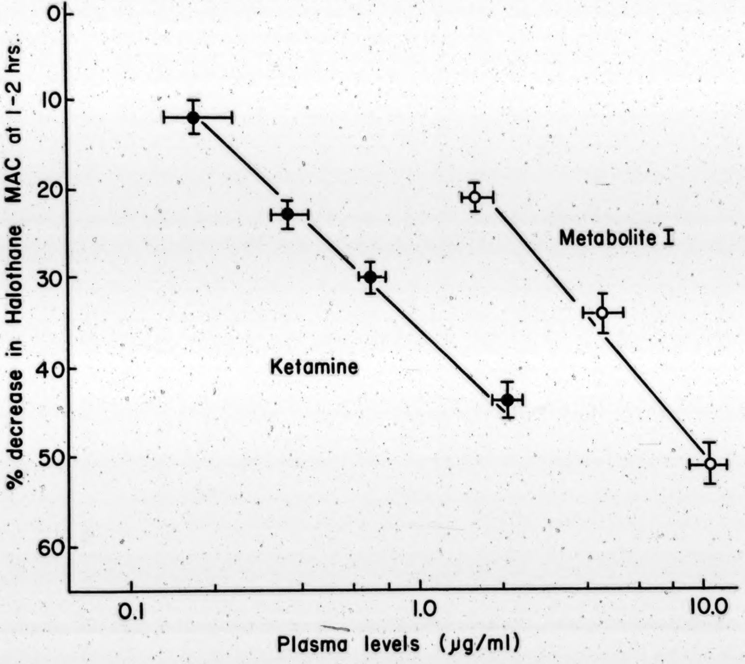

Figure 3-10. Correlations between plasma levels of ketamine or metabolite I and halothane MAC 1-2 after i.m. injection of ketamine or metabolite I, respectively. The effect of metabolite I formation has been subtracted from the measured decrease in MAC 1-2 after i.m. ketamine in order to demonstrate the effect due to ketamine alone. Values represent means for five animals ± S.E.M.

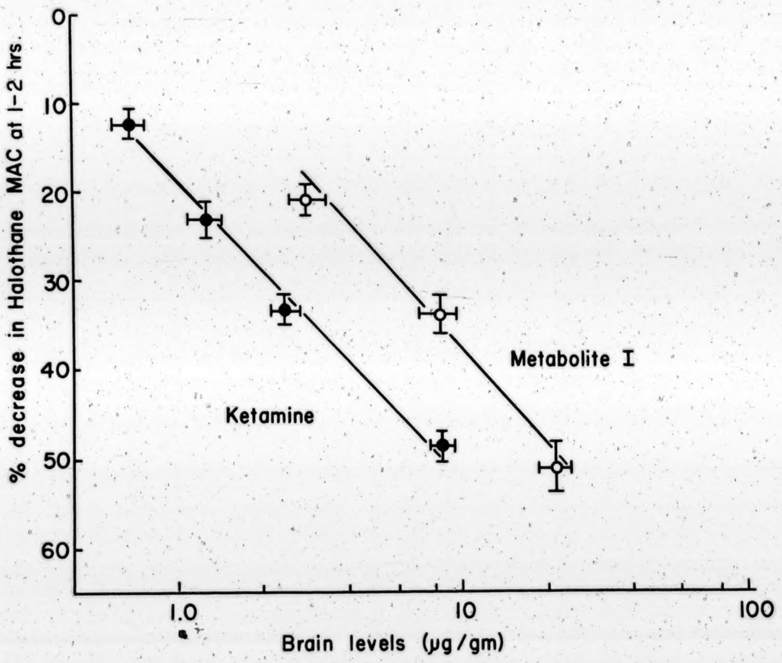

Figure 3-11. Correlations between brain levels of ketamine or metabolite I and halothane MAC after i.m. injection of ketamine or metabolite I, respectively. The effect due to metabolite I formation has been subtracted from the measured decrease in MAC 1-2 after i.m. ketamine in order to demonstrate the effect of ketamine itself. Values represent means ± S.E.M.

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TABLE 3-2

Levels of Metabolite II After I.M. Ketamine or Metabolite I During Halothane Anesthesia

Peak levels of metabolite II in the plasma and brain from one-to-four hours following intramuscular ketamine or metabolite I during halothane anesthesia. Samples were obtained and analyzed as described under "Materials & Methods." Values represent means ± S.E.M. for five animals.

	Dose (mg/kg)	Plasma (μg/ml)	Brain (μg/g)
Ketamine	5	0.12 ± 0.03	0
	10	0.22 ± 0.11	0
	20	0.66 ± 0.08	0.38 ± 0.16
	50	1.73 ± 0.33	1.94 ± 0.34
Metabolite I	20	0.46 ± 0.15	0.96 ± 0.13
	50	2.53 ± 0.43	3.59 ± 0.43
	100	4.66 ± 0.84	7.88 ± 0.51

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DISCUSSION

Ketamine and its principal metabolite both depressed halothane anesthetic requirement in a dose-dependent fashion (table 3-1). More importantly, significant depressions in halothane MAC were found at times when identical doses of ketamine or metabolite I administered alone had not observable pharmacologic effects (table 2-1). We have also correlated these depressions in halothane MAC with brain levels of ketamine and thereby, this represents the first report correlating alterations in anesthetic requirement with brain levels of a fixed agent.

These data do not support the suggestion that ketamine is a "short-acting" agent. Doses of ketamine producing less than ten minutes of hypnosis resulted in analgesia and ataxia lasting an hour or longer. Furthermore, we have demonstrated that subanesthetic doses of ketamine resulted in depression of halothane MAC for as long as six hours. The effects of ketamine in depressing the central nervous system, as reflected by decreases in anesthetic requirement, were of even longer duration than any of the apparent pharmacologic effects and occurred at relatively low levels of the drug. For example, ketamine levels in the rat brain were approximately 30 μg/g when the animal regained the righting reflex and 13 μg/g at the termination of the analgetic period following i.m. injection of ketamine (fig. 4-2), yet significant dose-related depressions of halothane anesthetic requirement were found at brain levels ranging from 0.1 to 10 μg/g (fig. 3-11).

The prolonged action of ketamine is due in part to persistence of ketamine, as a result of its high lipid solubility (Cohen & Trevor, 1974), and in part to the conversion of ketamine to metabolite I, which itself possesses weak anesthetic properties. We estimated that approximately 75-80% of the prolonged depression of anesthetic requirement following ketamine administration was attributable to ketamine itself and that the remaining 20-25% was related to the formation of metabolite I. Our estimates of the relative potency of metabolite I indicated a potency approximately three times that reported by previous investigators (Chang, et al, 1965; Chen, 1969; Chang & Glazko, 1974). They reported a potency ratio of 10:1 between ketamine and metabolite I, however we estimated a potency ratio of 3:1 from comparison of brain levels producing a 50% depression of MAC (fig. 3-11). This also agrees with the 3:1 ratio of the ketamine-to-metabolite I dose required to decrease MAC by 50% (fig. 3-2). The parallelism of the log dose-response curves for ketamine and metabolite I was consistent with a similar mechanism of action in their effects on halothane MAC.

Metabolite II has been reported to have 1/100 the anesthetic activity of ketamine (Chen, 1969; Chang & Glazko, 1974). Metabolite II was found in the plasma and brain following administration of the larger doses of ketamine, and all doses of metabolite I, although it was not found by other investigators following intravenous administration of equipotent doses of ketamine (Cohen et al, 1973; Cohen & Trevor, 1974). We have no explanation for this apparent discrepancy. Nevertheless, the levels of metabolite II we detected were significantly lower than the levels of either ketamine or metabolite I. Since no measurable brain levels of metabolite II were found after ketamine, 5 or 10 mg/kg i.m., and since the plasma and brain levels of metabolite II were relatively constant from one-to-four hours following ketamine, 20 or 50 mg/kg i.m. (unreported data), it would seem unlikely that metabolite II contributed significantly to the ketamine-induced depression of halothane MAC.

This study also suggested that halothane altered the actions of ketamine and metabolite I by influencing their biodisposition. This was evidenced by the alterations produced in the plasma, and hence brain, decay curves of ketamine and its principal metabolite. The specific changes in biodispostion that could produce this result include alterations in cardiac output and hence ketamine's uptake, distribution and/or redistribution, as well as a reduction in its metabolism. For example, a decrease in blood flow at the site of intramuscular injection of thiopental has been reported to slow the uptake and reduce the peak brain level, while elevating the levels in the brain 60-140 minutes after administration using computer model studies (Saidman & Eger, 1973).

In conclusion, demonstrated correlations between brain levels of ketamine or metabolite I and reductions in halothane MAC suggest that these two agents are jointly responsible for the lethargy seen clinically after recovery from the anesthetic effects of ketamine. The concomitant administration of a potent inhalational anesthetic (e.g. halothane) would be expected to prolong further the post-hypnotic lethargy associated with ketamine.

SUMMARY

The interaction of intramuscularly injected ketamine and its N-demethylated metabolite (metabolite I) with halothane was evaluated in rats. Five, 10, 20 or 50 mg/kg doses of ketamine alone or 20, 50 or 100 mg/kg doses of metabolite I alone produced less than ten minutes of hypnosis. However, halothane anesthetic requirement (i.e., MAC) was depressed in a dose-dependent fashion as much as 56% at 1-2 hours and as much as 14% at 5-6 hours after injection of ketamine, 50 mg/kg i.m. The reduction in MAC was correlated with brain levels of ketamine or metabolite I, suggesting a ketamine : metabolite I potency ratio of 3:1. The half-life of ketamine in plasma and brain appeared to be longer in the presence of halothane than when ketamine was given alone. It was concluded that ketamine is not a short-acting drug and that concomitant use with halothane might be expected to prolong further the duration of its action on the central nervous system.

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CHAPTER IV

EFFECTS OF HALOTHANE ANESTHESIA ON KETAMINE BIODISPOSITION

EFFECTS OF HALOTHANE ANESTHESIA ON KETAMINE BIODISPOSITION

Pathologic states such as circulatory and hepatic disease are known to alter the biodisposition of lipid-soluble drugs (Price, 1960; Stenson et al, 1971; Koch-Weser & Klein, 1971; Bellet et al, 1971; Thomson et al, 1973). It follows therefore that pharmacologic agents such as inhalational anesthetics, which are known to exert marked actions on the cardiovascular system (Goldberg, 1968; Eger et al, 1970) and on the hepatic microsomal drug-metabolizing systems (Brown, 1971 & 1972), may alter the disposition of another drug given concomitantly.

Previously discussed experiments evaluating pharmacological interactions between ketamine and halothane in the rat demonstrated that plasma and brain decay curves for ketamine were significantly altered in the presence of halothane anesthesia (figs. 3-6 & 3-7). In order to understand more completely the nature and significance of this observation, we attempted to answer the following questions.

First, does halothane anesthesia prolong the half-life of ketamine and if so, does this halothane-induced prolongation of ketamine half-life produce corresponding changes in the duration of its pharmacological effects? To answer these questions, the duration of ketamine-induced ataxia as well as tissue levels of ketamine, metabolite I and metabolite II were measured after ketamine administration to control and halothane-anesthetized animals.

Secondly, what are the precise effects of halothane on the uptake, distribution and redistribution of ketamine and its metabolites? The answer to this question was approached by determining tissue levels of ketamine and its principal metabolites after intramuscular or intravenous administration of ketamine in both control and halothane-anesthetized groups.

Thirdly, what is the effect of halothane on the metabolism of ketamine and metabolite I? Effects of various concentrations of halothane on both the in vivo and in vitro metabolism of ketamine were examined and the kinetics of this interaction were evaluated. Similarly, the in vitro metabolism of metabolite I was studied in the presence, as well as in the absence, of halothane.

Finally, is prolongation of ketamine half-life by halothane related in any way to an effect of the gas anesthetic on renal elimination of the drug or its metabolites? The rate of urinary excretion of ketamine and its principal metabolites was investigated in the presence and absence of halothane anesthesia. The effects on ketamine biodisposition of alterations (i.e., biliary tract obstruction or nephrectomy) in the major excretory pathways for ketamine and its degradation products also were evaluated.

MATERIALS & METHODS

Animal experiments:

In order to study the effects of halothane anesthesia on the duration of ataxia, male Sprague-Dawley rats (250-300 g) were divided into three groups. The control group received ketamine, 50 mg/kg i.m., in the right hamstring muscles. The duration of ataxia (i.e., abnormal gait) was measured with zero time taken as the end of the injection. Subgroups of five rats each were sacrificed at various time intervals. Blood obtained by direct cardiac puncture was heparinized and centrifuged for five minutes at 1,000 x g to obtain plasma for analysis of ketamine and its metabolites as described earlier. Immediately after cardiac puncture, animals were decapitated and the cerebral hemispheres were transferred to ice where superficial blood vessels were removed. One part tissue was added to nine parts 0.1N HCl, homogenized with a Polytron PT 10 (Kinematica Gmbh, Luzern, Switzerland) and centrifuged at 100,000 x g for sixty minutes to obtain supernatant for drug analysis. The second group of rats was anesthetized with halothane, tracheostomies were performed, and the level of halothane was allowed to stabilize at an "alveolar" concentration of 0.8% v/v halothane in oxygen as described in the appendix. Ketamine 50 mg/kg i.m. was administered, sixty minutes later the animals were allowed to recover from the halothane anesthesia (while breathing an oxygen/carbon dioxide mixture) and the duration of ataxia was determined as before. End-tidal gas samples obtained from halothane anesthetized animals at the termination of the ataxic period were estimated to contain less than 0.08% halothane. The third group was continuously anesthetized with 0.8% halothane in oxygen. Ketamine, 50 mg/kg i.m., was injected after completion of the tracheostomy and stabilization of the end-tidal anesthetic concentration, and subgroups of five rats each were sacrificed at various time intervals as described above. Plasma and brain half-life values were calculated as the time required for the drug level to decrease to 50% of the peak level.

To investigate the uptake and distribution pattern of i.m. ketamine alone and in the presence of halothane, rats (250-300 g) were divided into two groups. Controls were injected with ketamine, 50 mg/kg i.m., and five animals were sacrificed and blood obtained at each of several time intervals, as in the previously described groups. Additionally, portions of all lobes of the liver, both kidneys, white (perinephric) fat, and adductor magnus/gastrocnemius/soleus muscle groups (on the non-injected side), as well as the cerebral hemispheres were obtained and 10% w/v tissue homogenates prepared as described above. Identical experiments were performed on a second group of animals continuously anesthetized with 0.8% halothane.

The distribution of ketamine administered intravenously in the presence of halothane anesthesia was studied using smaller rats (100-120 g) divided into two groups. Control animals were injected with ketamine, 30 mg/kg i.v., via the tail vein and decapitated at various time intervals, with blood samples obtained by exsanguination. Tissue supernatants (brain, liver, kidney, skeletal muscle, cardiac muscle, and skin/subcutaneous tissue) were prepared and assayed as previously described. The second group of rats was continuously anesthetized with 0.8% halothane and plasma and tissue supernatant samples were obtained at the same time intervals as for the control group.

In order to investigate the effects of halothane on the in vivo metabolism of ketamine, rats (100-120 g) were divided into three groups. In the control group, each animal was injected with ketamine, 30 mg/kg i.v., and sacrificed after twenty minutes. After obtaining blood by exsanguination, the remainder of the animal was homogenized in 0.1N HCl to obtain a 10% w/w "whole animal" homogenate. In the second and third groups, animals were anesthetized and the halothane concentrations maintained at 0.8% and 1.6%, respectively. The rats were sacrificed twenty minutes after ketamine injection and plasma and whole animal supernatant samples were prepared as described above.

Urinary excretion of ketamine, metabolite I and metabolite II was studied in the control situation as well as in the presence of 0.8% halothane anesthesia. Control rats (250-300 g) were injected with ketamine, 50 mg/kg i.m., and sacrificed after either one or two hours. Urine was collected during the time intervals studied (residual urine was emptied by direct withdrawal from the bladder after sacrificing the animal). The halothane-treated group was anesthetized as before and urine samples were obtained by direct withdrawal from the bladder at 60 or 120 minutes after ketamine, 50 mg/kg i.m.

The effect of biliary tract occulsion on urinary excretion of ketamine and its metabolites was studied using rats divided into four groups, two of which were anesthetized with halothane. One control group ("sham") was rapidly anesthetized with a 50% cyclopropane in oxygen mixture and a laparotomy was performed during which time the common bile duct was identified but not manipulated. The animals recovered rapidly from the cyclopropane anesthesia and were injected with ketamine, 50 mg/kg i.m., and urine then was collected at hourly intervals for analysis of ketamine and its major metabolites. In the second control group ("bile duct ligation") the animals were again anesthetized with cyclopropane, a laparotomy was performed, and the bile duct ligated at two levels with 4-0 suture silk. The animals were subsequently treated as described above following a rapid recovery from the effects of cyclopropane. The two halothane anesthetized groups were handled in an analogous manner. Both halothane groups underwent laparotomy for purposes of performing either a sham operation or a bile duct ligation. The halothane concentration was stabilized at 0.8% halothane in oxygen, the bladder was catheterized with a thin (KA) polyethylene tubing and urine was collected at various intervals following ketamine, 50 mg/kg i.m.

Similarly, the effect of bilateral nephrectomy on bilary excretion of ketamine and its metabolites was studied under halothane anesthesia. Two groups were anesthetized with halothane and subjected to either a sham operation or a bilateral nephrectomy. Both groups of animals were anesthetized and the kidneys were isolated without difficulty via a posterior approach. In the nephrectomized group, the renal artery and vein were ligated and divided bilaterally, but the kidneys remained *in situ* and the wound was closed in a conventional manner. A laparotomy then was performed and the bile duct was isolated and cannulated with PL-50 polyethylene tubing from which bile was collected. The incision was closed and the animals were subsequently injected with ketamine, 50 mg/kg i.m., after stabilization at an end-tidal halothane concentration of 0.8% in oxygen. The bile was collected over various time intervals and analyzed for ketamine and its metabolites as described above.

In vitro experiments :

The *in vitro* metabolism of ketamine by rat hepatic tissue was examined using post-mitochondrial supernatant and microsomal fractions prepared according to a modified version of the procedure described by Fouts (1971). Liver homogenates (10% w/v) were prepared in a 50 mM Tris-HCl/160 mM KCl (pH 7.4) buffer and centrifuged at 9,000 x g for twenty minutes with the supernatant subsequently recentrifuged at 9,000 x g for an additional 15 minutes to obtain post-mitochondrial supernatant. Microsomes were sedimented by centrifugation of the post-mitochondrial supernatant at 105,000 x g for 60 minutes,

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with the microsomal pellet resuspended in 50 mM Tris-HCl/160 mM KCl buffer.

In the studies using the post-mitochondrial supernatant fraction, reaction vessels containing 0.9 ml of a 50 mM Tris-HCl/160 mM KCl (pH 7.4) buffer, 0.6 ml of buffer containing nicotinamide (4 mM), MgCl2 (10 mM) and glucose-6-phosphate (5 mM), and 0.8 ml of post-mitochondrial supernatant (6-10 mg protein/ml supernatant as determined by the method of Lowry et al, 1951) were allowed to equilibrate for fifteen minutes at 37° C in the presence of either oxygen or a halothane-oxygen mixture directed into each sample flask on a Dubnoff metabolic incubator. Following the preincubation period, 0.1 ml of NADP (1 mmol) was added and the reaction initiated by the addition of of 0.1 ml of ketamine hydrochloride (various concentrations). Samples (0.1 ml) were withdrawn at zero time and after 10 and 20 minutes, transferred into 0.9 ml of 0.1N HCl, and subsequently extracted for assay of ketamine and its metabolites. The initial ketamine concentrations varied from 5 to 100 μg/ml reaction medium and the concentrations of halothane studied varied from 0.8 to 4.4%.

In the kinetic studies utilizing liver microsomes, reaction vessels contained 0.9 ml of a 50 mM Tris-HCl/160 mM KCl (pH 7.4) buffer, 0.5 ml of buffer containing MgCl2 (25 mmol) and glucose-6-phosphate (12.5 mmol), 0.1 ml of glucose-6-phosphate dehydrogenase (1 I.E.U.) and 0.8 ml of microsomal suspension (1-3 mg of protein per ml of reaction medium). The reaction was subsequently carried out as described above. The initial ketamine concentrations varied from 0.42 to 6.3 μM and the concentrations of halothane studied varied from 0.8 to 12.8%. Assuming an Ostwald solubility coefficient of 0.8 (Steward et al., 1973) for halothane at 37° C, a 1% v/v halothane gas vapor (0.388 mM) would result in a halothane concentration of 0.310 mM in the reaction medium at equilibrium under our experimental conditions. This prediction was confirmed using a gas-liquid chromatograph to determine the halothane concentration in the reaction medium. Inhibition of ketamine metabolism by halothane was studied using Lineweaver-Burk (1934) and Dixon (1953) plots calculated by the least-squares method of linear regression analysis, from which the Michaelis constant (Km), inhibitor constant (Ki) and maximal velocity (Vmax) were calculated.

The in vitro metabolism of metabolite I was studied using both post-mitochondrial and liver microsomal preparations as described above. A control group of reaction vessels was exposed to oxygen while the experimental group was equilibrated with a 1.6% halothane in oxygen mixture. The initial metabolite I concentration varied from 0.21 to 6.3 µM. The reaction was was initiated by the addition of 0.1 ml of metabolite I (various concentrations) and samples (0.1 ml) were obtained as before for determination of metabolite I and metabolite II.

Assay of ketamine and its metabolites:

The method of extraction and analysis was according to a modified version of the GLC procedure of Chang and Glazko (1972) described earlier. Duplicate assays again demonstrated good reproducibility with a variation of ±3%, and standard curves were prepared for each series of analyses. When the drug or its metabolites were added to various tissue homogenates, the analytical recoveries ranged from 96 to 100%.

Statistical methods:

The mean and S.E. of each variable, for every group of rats, were calculated at each time period. Means were compared by unpaired Student's t-test and differences with $P<0.05$ were considered significant.

Chemicals:

All reagents were obtained from available commercial sources. Halothane (Fluothane) was generously supplied by Ayerst Laboratories (New York, NY), while ketamine hydrochloride (Ketalar) as well as metabolites I and II were gifts from Parke, Davis & Company (Detroit, Mich).

RESULTS

Correlations between ketamine levels and duration of pharmacologic effects:

Plasma and brain ketamine decay curves after ketamine administration (50 mg/kg i.m.) are shown in figure 4-1. In the presence of continuous halothane anesthesia, the half-lives were prolonged as predicted from our earlier studies. After the animals were allowed to recover from the anesthetic effects of halothane sixty minutes following the ketamine injection, slopes of the decay curves more closely approximated those of the control group. The duration of ataxia in the control group was 51.2 ± 3.2 minutes corresponding at recovery to a plasma level of 2.0 μg/ml and a brain level of 8.4 μg/g tissue. In the group exposed to halothane for sixty minutes, the duration of the ataxic period was 94.9 ± 5.4 minutes with plasma and brain levels, at recovery from ataxia, of 1.7 μg/ml and 7.6 μg/g, respectively. This suggested that the residual halothane present in the brain did not contribute significantly to the ataxia at that time. Although brain levels of halothane were not measured, end-tidal halothane concentrations were less than 0.08% at the termination of the ataxic period, a value which is less than 1/10 of that employed during the halothane anesthesia period. It is of interest to note that the residual halothane (approximately 10% of the experimental concentration) produced a corresponding 10% reduction in the brain level of ketamine at the termination of the ataxic period.

The duration of hypnosis after ketamine, 50 mg/kg i.m., in the unanesthetized control group was 10.1 ± 1.1 minutes, corresponding to a plasma level of 7.4 μg/ml and a brain level of 30.5 μg/g at the time the animals regained the righting reflex (fig. 4-2). These values correspond closely to to those reported earlier following i.v. ketamine (Cohen et al., 1973). The

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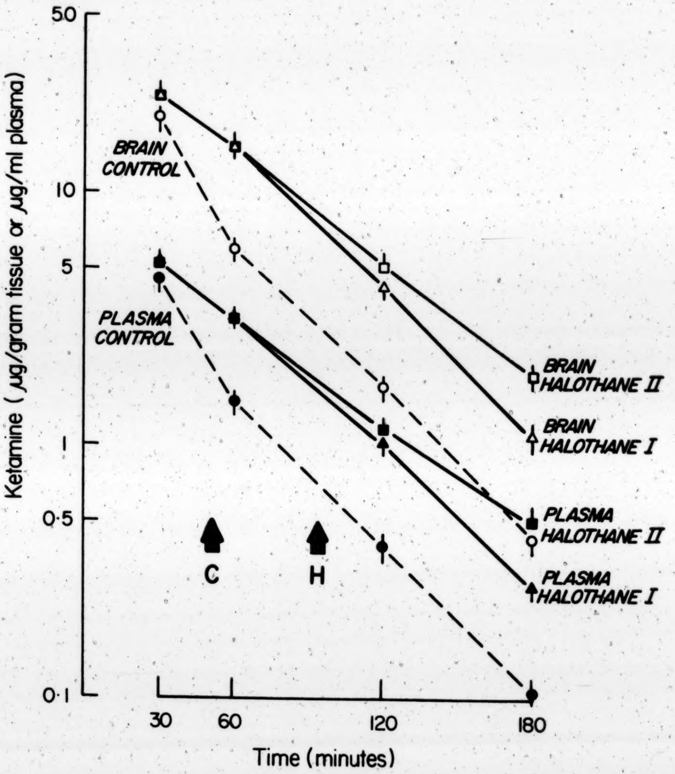

Figure 4-1. Plasma and brain levels of ketamine on a logarithmic scale as a function of time after ketamine (50 mg/kg i.m.) in unanesthetized animals (controls), in rats exposed to anesthesia during the first sixty minutes only (halothane I), and in animals continuously anesthetized (halothane II). Time to the termination of ataxia for control (C) and halothane I (H) groups are indicated by arrowheads. Values are means of five animals and the vertical bars represent ± S. E. M.

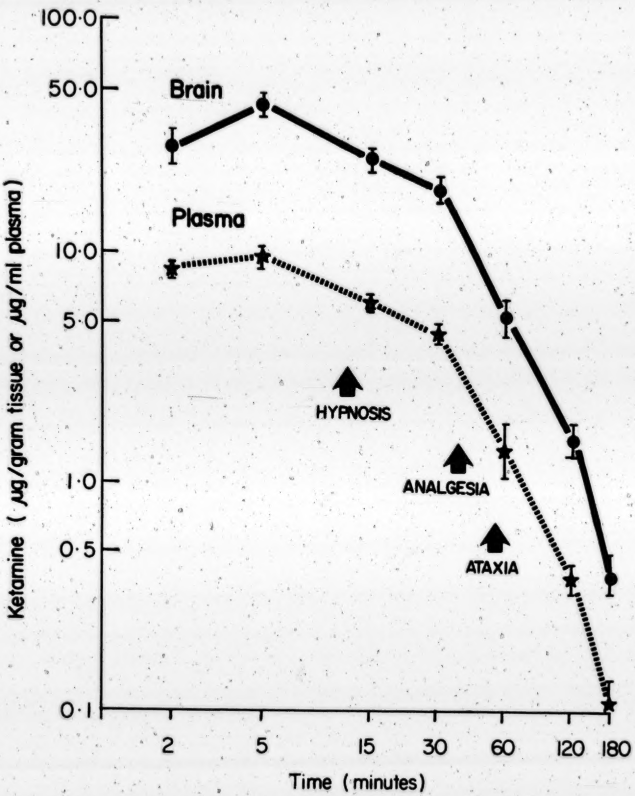

Figure 4-2. Plasma and brain levels of ketamine as a function of time after ketamine (50 mg/kg i.m.) in unanesthetized animals. The times to the termination of hypnosis, analgesia and ataxia are indicated by the arrowheads. At the indicated times, rats were sacrficed and plasma and brain samples obtained for GLC assay of ketamine as described under "Materials & Methods." The values are means of five animals at each time period and vertical bars represent ± S.E.M.

duration of analgesia (altered responsiveness to a painful mechanical stimulus) in this same group of rats was 39.1 ± 3.2 minutes and corresponded to a plasma level of 2.9 μg/ml and a brain level of 12.7 μg/g at the termination of the analgetic period (fig. 4-2).

Influence of halothane on the uptake and distribution of i.m. ketamine:

Tissue distribution of ketamine after an i.m. injection is shown in figure 4-3. Ketamine was rapidly absorbed from the i.m. site of injection as evidenced by the fact that peak brain and plasma levels were attained within five minutes. Initially, ketamine was distributed to the brain and other highly perfused tissues (e.g., kidney). The distribution of ketamine into skeletal muscle followed a slightly more prolonged time course, reaching a maximum level from 5 to 30 minutes after the injection. Subsequently, ketamine "redistributed" into less well perfused tissues such as fat (peak level attained from 30-60 minutes after injection), where the levels were rising during a time interval in which they were falling in brain and plasma. A similar distribution and redistribution pattern was seen following the intravenous route of administration (fig. 4-5).

Effects of 0.8% halothane on the distribution of i.m. ketamine is also shown on figure 4-3. Halothane delayed the attainment of peak plasma levels and prolonged the plasma half-life from 20 to 45 minutes. The peak plasma level achieved in the presence of halothane was 6.2 μg/ml in contrast to 9.9 μg/ml in the control situation. As expected, a delay in the achievement of peak brain levels and a prolongation of brain half-live from 20 to 50 minutes was found in the presence of halothane anesthesia. The peak brain ketamine level (29.0 μg/g) in the halothane-anesthetized group was significantly lower than in the control group (44.5 μg/g). Effects of halothane on ketamine levels in the kidney were similar to those above. Although halothane slowed the rate of

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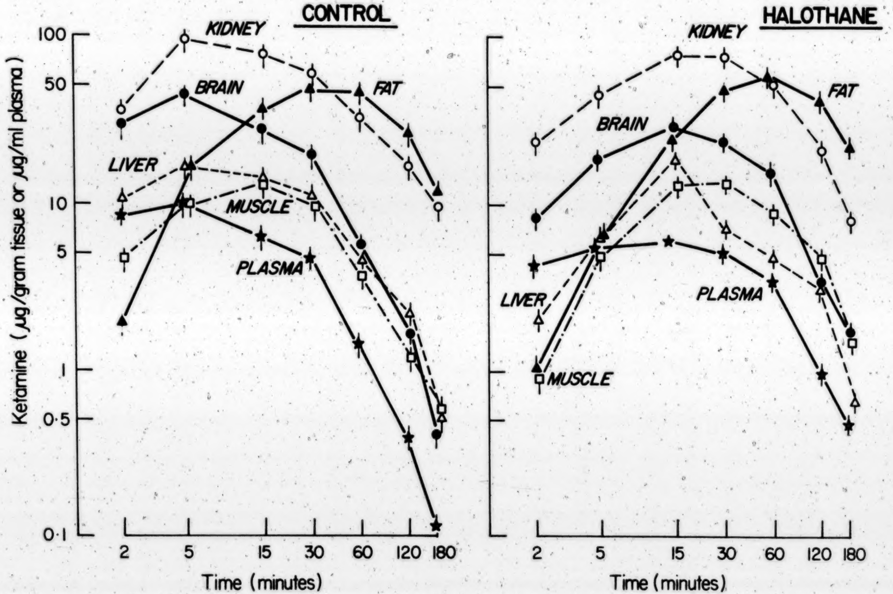

Figure 4-3. Plasma and tissue levels of ketamine as a function of time after ketamine administration (50 mg/kg i.m.) in unanesthetized (control) animals and in rats continuously anesthetized with halothane (halothane). At the indicated times, rats were sacrificed and tissue samples obtained for GLC assay of ketamine as described under "Materials & Methods." Values are means of five animals and the vertical lines represent ± S.E.M.

uptake of ketamine into the liver, muscle and fat, the peak levels achieved were not significantly different from those of the control group. It was noted that at the point of peak tissue levels, tissue/plasma ratios for ketamine as well as metabolites I and II tended to be higher in the presence of halothane anesthesia (table 4-1).

Data regarding metabolite I levels and its disposition after administration of i.m. ketamine are summarized in table 4-2. Tissue uptake and the time to achievement of peak levels, as well as tissue half-life values for metabolite I were prolonged by halothane. Furthermore, the peak levels of metabolite I were lower in all tissues when ketamine was administered during halothane anesthesia.

The highest levels of metabolite II following i.m. ketamine were found in liver and kidney tissues with lesser amounts in the brain, plasma and muscle (fig. 4-4). During the first hour of halothane anesthesia, levels of metabolite II in the liver and muscle were significantly lower than control values. On the other hand, kidney levels tended to be elevated during the early time periods under halothane anesthesia. Levels of metabolite II in all tissues studies tended to plateau from 60 to 180 minutes in the presence of halothane, in contrast to control levels which were found to fall sharply during this same time interval. Metabolite II was not detected in fat at any any time in either control or halothane anesthetized groups, implying that it is significantly less lipid soluble than either ketamine or metabolite I.

Effects of halothane on the distribution of i.v. ketamine:

To assess the possible contribution of halothane-induced alterations in the rate of absorption from the intramuscular site of injection into the plasma, tissue disposition of ketamine was studied after the intravenous route of admin-

TABLE 4-1

Tissue/plasma Partition Coefficients for Ketamine and Metabolites I and II

The time to attainment of peak tissue levels (mins.) and the tissue/plasma ratios at this time following ketamine, 50 mg/kg i.m., were determined in control and halothane-anesthetized animals as discussed in "Materials & Method" section. Values represent means ± S.E.M. for five animals at each time point.

Tissue	Ketamine				Metabolite I				Metabolite II			
	Control		Halothane		Control		Halothane		Control		Halothane	
	time/ratio		time/ratio		time/ratio		time/ratio		time/ratio		time/ratio	
Brain	5	4.47	15	4.75	30	1.46	60	1.72	15	2.69	15	4.18
Fat	30	10.13	60	17.19	60	3.75	60	4.73	-	-	-	-
Kidney	5	9.44	15	13.63	30	6.39	30	8.06	15	3.89	15	6.30
Liver	5	1.65	15	2.95	30	10.49	30	10.61	15	7.65	30	8.13
Muscle	15	1.78	15	2.30	30	0.75	60	1.08	30	1.27	60	1.32

TABLE 4-2

Tissue Distribution of Metabolite I after Intramuscular Administration of Ketamine

Levels of metabolite I in tissue samples were measured at various time intervals from 2 to 180 minutes after ketamine, 50 mg/kg i.m., according to procedures detailed in the "Materials & Methods" section. The time to attainment of peak level, the actual peak level achieved, and the half-life were determined. Values represent means ± S.E.M. for five animals at each time interval.

Tissue	Control			Halothane		
	time to peak (min.)	peak level (µg/ml or g)	half-life (min.)	time to peak (min.)	peak level (µg/ml or g)	half-life (min.)
Plasma	30	4.1 ± 0.4	60	60	2.6 ± 0.2	110
Brain	30	5.9 ± 0.6	50	60	4.4 ± 0.3	75
Kidney	30	26.0 ± 2.1	120	30	21.3 ± 1.8	150
Liver	30	62.9 ± 3.0	40	30	28.1 ± 1.2	105
Muscle	30	3.1 ± 0.3	30	60	2.7 ± 0.2	115
Fat	60	12.7 ± 1.4	25	60	10.2 ± 1.2	60

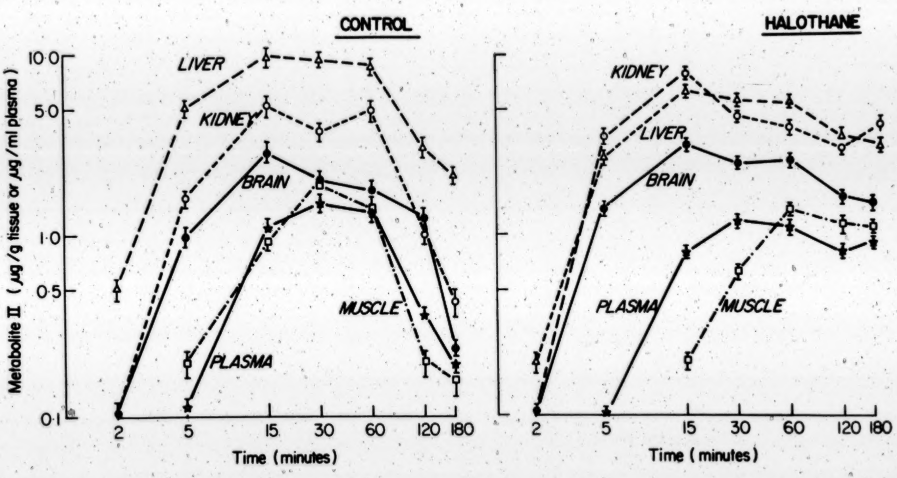

Figure 4-4. Plasma and tissue levels of metabolite II as a function of time after ketamine administration (50 mg/kg i.m.) in unanesthetized controls and in animals continuously anesthetized with halothane. At the indicated times, rats were sacrificed and tissue samples obtained for GLC assay of metabolite II as described under "Materials & Methods." The values are means of five animals and vertical lines represent ± S.E.M.

istration as shown in figure 4-5. Drug levels in plasma, brain and muscle were significantly higher in the presence of halothane from 20 to 60 minutes after the injection. Under halothane anesthesia, muscle levels were reduced during the initial ten minute time period and skin/subcutaneous tissue levels were significantly lower than controls from 20 to 60 minutes after the injection. Levels of metabolite I in plasma, muscle and skin were significantly lower in the halothane group from 20 to 60 minutes after i. v. ketamine (fig. 4-6). Metabolite II was only detected in plasma after i. v. ketamine; however, the level was reduced significantly in the presence of halothane anesthesia (data not shown).

Ketamine and metabolite I metabolism in the presence of halothane anesthesia:

The effects of halothane on *in vitro* metabolism of ketamine by liver post-mitochondrial supernatant are summarized in table 4-3. Halothane caused a concentration-dependent decrease in the rate of ketamine N-demethylation. In a preliminary study, the rate of metabolite I degradation by hepatic post-mitochondrial supernatant was found to be markedly reduced compared to the N-demethylation of ketamine and it was further decreased in the presence halothane (unreported data). The enzyme kinetics of these metabolic reactions were studied using an hepatic microsomal preparation.

The effects of halothane on *in vitro* metabolism of ketamine by liver microsomes are summarized graphically in figure 4-7. Halothane caused a concentration-dependent decrease in the rate of ketamine N-demethylation. The halothane gas concentration producing a 50% inhibition of this reaction was estimated to be 5.1%. The microsomal N-demethylation of ketamine in the presence of halothane followed noncompetitive kinetics with a Km of 0.10 mM and a Ki equal to 1.56 mM (fig. 4-8 & 4-9). Similarly, metabolite I

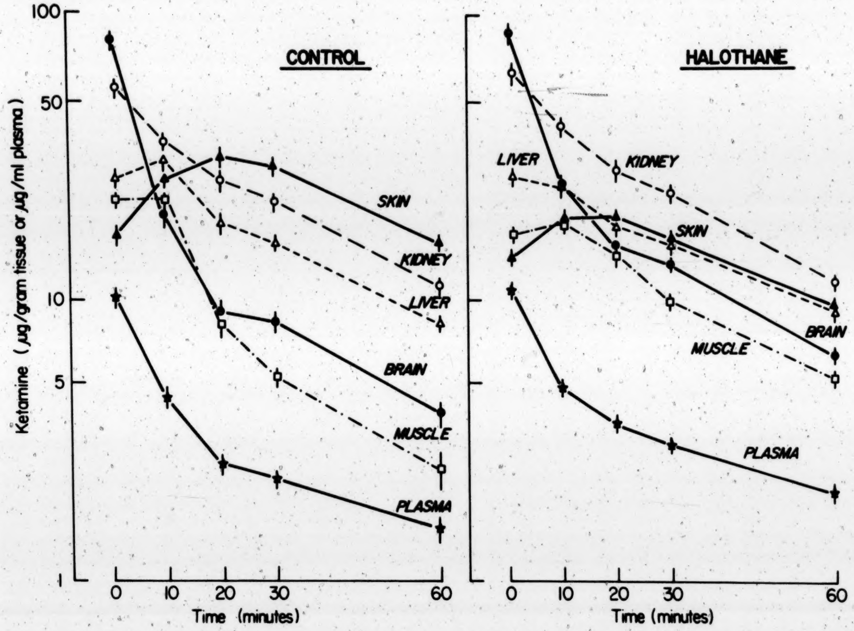

Figure 4-5. Plasma and tissue levels of ketamine as a function of time following ketamine administration (30 mg/kg i.v.) in unanesthetized (control) animals and in rats continuously anesthetized with halothane (halothane). At the indicated times, rats were sacrificed and tissue samples obtained for GLC assay of ketamine as described under "Materials & Methods." Values are means of four animals and the vertical lines represent ± S. E. M.

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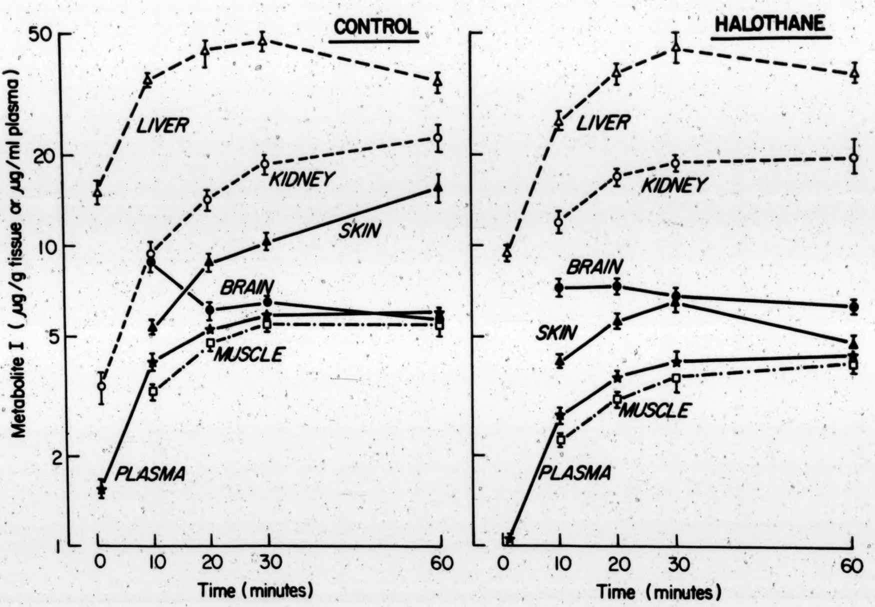

Figure 4-6. Plasma and tissue levels of metabolite I as a function of time after ketamine administration (30 mg/kg i.v.) in unanesthetized controls and in animals continuously anesthetized with halothane. Rats were sacrificed at the indicated time intervals and samples were obtained for GLC assay of metabolite I as described under "Materials & Methods." The values are means of four animals and the vertical lines represent ± S.E.M.

TABLE 4-3

Effect of halothane on In Vitro Metabolism of Ketamine by Liver Post-Mitochondrial Supernatant

The rate of metabolism of ketamine by rat liver post-mitochondrial supernatant was estimated as detailed under "Materials & Methods." The average rate of ketamine degradation, utilizing initial ketamine concentrations from 2.7 to 14.3 µmol/g liver, was calculated for each of four experiments using four different halothane concentrations. Values represent means ± S. E. M.

Experimental groups	Rate of ketamine metabolism (nmol/g tissue/min) Control	Halothane	Percentage decrease in the rate of ketamine metabolism
0.8% Halothane	225 ± 17	204 ± 14	9.3 ± 0.9
1.1% Halothane	242 ± 30	202 ± 24	16.5 ± 3.3
2.2% Halothane	209 ± 11	148 ± 10	29.2 ± 1.2
4.4% Halothane	222 ± 27	129 ± 16	41.9 ± 2.5

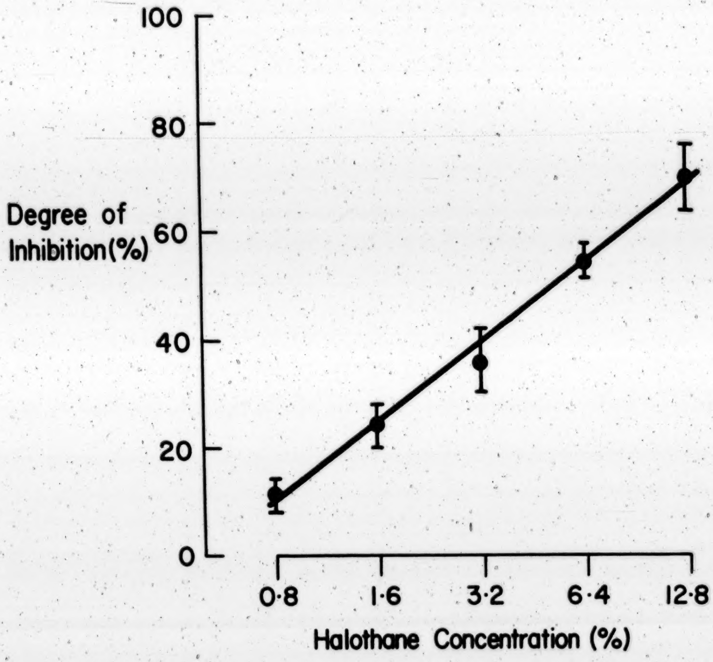

Figure 4-7. The percentage inhibition of hepatic microsomal N-demethylation of ketamine by halothane-oxygen gas mixture (on logarithmic scale) as described under "Materials & Methods." The line was plotted from calculations employing the least-squares method of linear regression analysis, with vertical bars representing ± S. E. M.

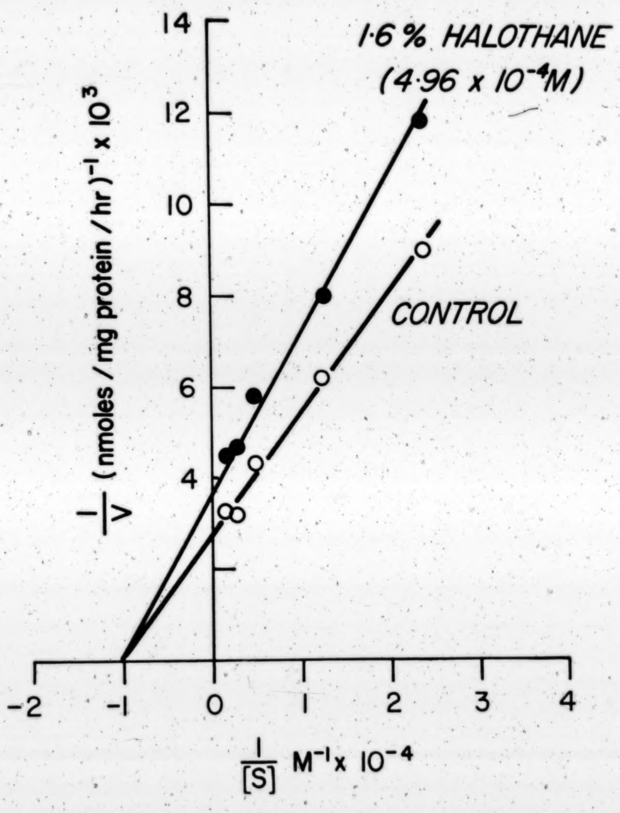

Figure 4-8. Lineweaver-Burk plot of halothane inhibition of ketamine N-demethylation using an hepatic microsomal preparation as described under "Materials & Methods." Lines were plotted from calcuations employing the least-squares method of linear regression analysis.

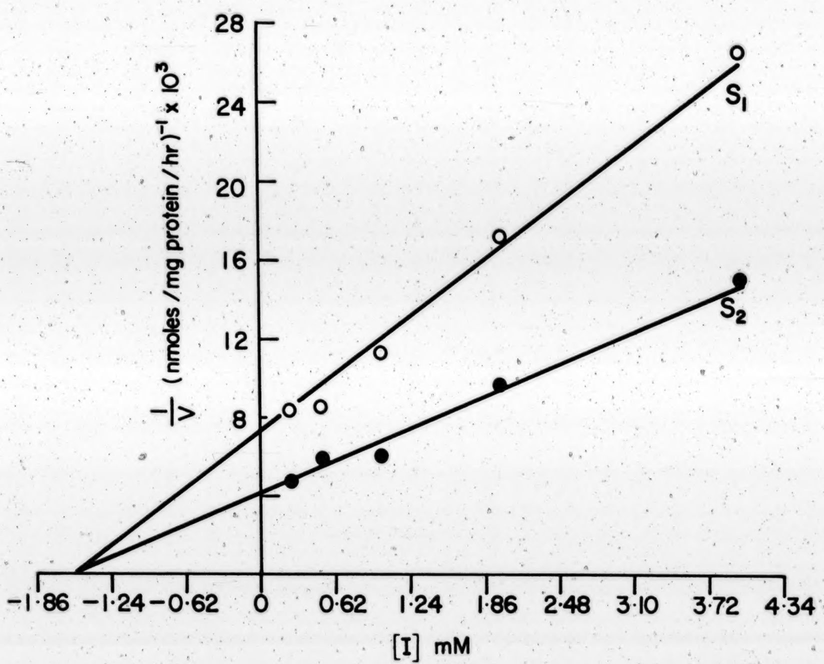

Figure 4-9. Dixon plot of halothane inhibition of ketamine N-demethylation using hepatic microsomal preparations as described under "Materials & Methods." The lower concentration of substrate (S1) was 0.817 μM and the higher concentration (S2) was 2.160 μM. Lines were plotted from calculations employing the least-squares method of linear regression analysis.

degradation by the hepatic microsomal preparation was inhibited in a non-competitive manner by halothane with a Km of 0.11 mM and a Ki equal to 1.64 mM (fig. 4-10). The maximal velocity (Vmax) for the oxidation of metabolite I in the absence of halothane (160 nmol/mg of protein per hour) was only 44% of Vmax for the N-demethylation reaction (365 nmol/mg protein/hr) under similar conditions.

Influence of halothane on the whole animal levels of ketamine & its metabolites:

Effects of halothane on the overall rate of *in vivo* metabolism of i.v. ketamine are summarized in table 4-4. Halothane produced dose-dependent increases in plasma and whole animal ketamine levels while decreasing levels of metabolites I and II. The total recovery of ketamine, metabolite I and metabolite II accounted for 87 to 91% of the injected dose at twenty minutes in the control group. In the presence of 0.8% and 1.6% halothane, total recoveries were 95 to 98% and 97 to 100%, respectively.

Effect of halothane on rate of excretion of ketamine and its metabolites:

The rates of urinary excretion of ketamine, metabolite I and metabolite II are summarized in table 4-5. In the first sixty minutes approximately 2% of the injected i.m. dose was recovered in the urine as the drug or one of its primary metabolites, with ketamine accounting for only 0.4%. Thus, although high concentrations of ketamine were found in kidney tissue (figs. 4-3 & 4-5), only small amounts of the drug were excreted unchanged in the urine during the early phases of its biodisposition.

During the first hour of halothane anesthesia, the rate of urine formation was only 25% of the control value. Furthermore, rates of urinary excretion of ketamine, metabolite I and metabolite II were reduced an average of 9%,

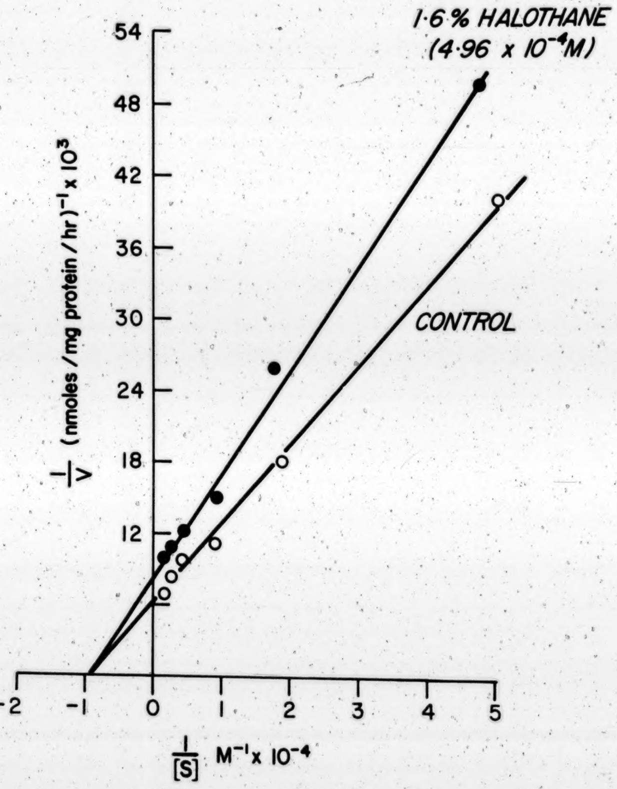

Figure 4-10. Lineweaver-Burk plot of halothane inhibition of metabolite I degradation using an hepatic microsomal preparation as described under "Materials & Methods." Lines were plotted from calculations employing the least-squares method of linear regression ananlysis.

TABLE 4-4

Effect of Halothane on Overall Rate of Ketamine Metabolism *In Vivo*

Levels of ketamine (K.), metabolite I (M.I.) and metabolite II (M.II.) were measured in plasma as well as in the "whole animal" at twenty minutes after ketamine, 30 mg/kg i.v., in unanesthetized (control) animals as well as in the presence of 0.8% and 1.6% halothane as described in the "Materials & Methods" section. Values are means ± S.E.M.

Experimental groups	Plasma levels (µg/ml)			Whole animal levels (µg/g)		
	K.	M.I.	M.II.	K.	M.I.	M.II.
Control	3.16±.42	6.38±.17	0.52±.08	14.93±.97	9.22±.32	0.75±.14
0.8% Halothane	4.48±.25*	5.17±.32*	0.50±.07	17.82±1.02	8.46±.60	0.63±.13
1.6% Halothane	5.72±.49*	4.90±.35*	0.46±.08	18.63±.88*	8.33±.36*	0.22±.10*

* P-value < 0.05 by unpaired Student's t-test

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TABLE 4-5

Effect of Halothane Anesthesia on the Rate of Urinary Excretion of Ketamine and Its Principal Metabolites

Urine was collected during the first two hours following ketamine, 50 mg/kg i.m., in unanesthetized (control) rats and animals continuously anesthetized with 0.8% halothane. The rate urine formation in the control animals was 100-125 µl/kg/min in contrast to 25-30 µl/kg/min in the presence of halothane anesthesia. Concentrations of ketamine, metabolite I and metabolite II were measured by GLC assay as detailed under "Materials & Methods." Values represent means ± S.E.M. for five animals.

Experimental group	Time interval (min.)	Rate of urinary excretion (µg/min) Ketamine	Metabolite I	Metabolite II
Controls	0 - 60	0.80±.14	2.33±.28	0.45±.07
	60 - 120	1.16±.32	3.59±.37	0.84±.08
0.8% Halothane	0 - 60	0.73±.09	0.57±.09*	0.25±.04*
	60 - 120	1.19±.26	2.15±.34*	0.76±.10

* P-value < 0.05 by unpaired Student's t-test

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76% and 44%, respectively, under halothane anesthesia (table 4-5). In the second hour, 3% of the injected dose was recovered from the urine in control animals. Rates of ketamine and metabolite II excretion in the urine were not changed significantly by halothane anesthesia from 60 to 120 minutes after the injection; however, the rate of metabolite I excretion was decreased by 40%.

In a separate experiment, it was found that less than 3% of the injected dose of ketamine, 50 mg/kg i.m., was recovered from the bile as the parent compound during the first sixty minutes in halothane-anesthetized rats with cannulated common bile ducts (table 4-6). During the second sixty minute time interval, less than 2% of the injected dose was secreted into the bile as the parent compound. Overall, 5-10% of the injected dose of ketamine was excreted into the bile per hour as either ketamine, metabolites I and II or their glucuronide conjugates. In addition, the recovery of ketamine from all gut tissue (including intraluminal contents) at thirty minutes was only 6-8% of the administered dose in control animals (unreported data). Thus, while halothane may influence biliary secretion, biliary clearance of ketamine is probably of minor importance in its overall biodisposition.

The effects of surgically-induced alterations in the normal excretory pathways are summarized in tables 4-6 & 4-7. Occlusion of the common bile duct significantly enhanced the rate of urinary excretion of ketamine and its metabolites, both in the presence as well as the absence of halothane anesthesia. The procedure produced only minimal elevations in plasma ketamine concentrations; nevertheless, marked elevations in plasma levels of the two principal metabolites were noted (unreported data). Bilateral nephrectomy produced a non-significant increases in the initial rates of biliary excretion of ketamine and its metabolites. However, at more prolonged time periods, the rates of biliary excretion of ketamine and metabolite I were enhanced in the

TABLE 4-6

Effects of Biliary Duct Occlusion on Urinary Excretion of Ketamine and Its Metabolites

Urine was collected during the first two hours after ketamine administration, 50 mg/kg i.m., in unanesthetized (control) rats and animals continuously anesthetized with 0.8% halothane following either a sham procedure (exploratory laparotomy) or a biliary duct ligation as detailed in the "Materials & Methods" section. The rate of urine in the control animals was significantly higher (100 µl/kg/min) than in the halothane anesthetized group (25 µl/kg/min). Values are means ± S.E.M. for four animals.

	Time interval (min.)	Rate of urinary excretion (µg/min)		
		Ketamine	Metabolite I	Metabolite II
Control groups:				
S/P Sham	0-60	1.01 ± .12	2.69 ± .33	0.33 ± .08
Operation	60-120	1.29 ± .23	2.88 ± .34	0.65 ± .09
S/P Biliary	0-60	2.44 ± .19*	5.36 ± .31*	1.07 ± .13*
Duct Ligation	60-120	2.70 ± .31*	7.73 ± .40*	1.93 ± .15*
Halothane groups:				
S/P Sham	0-60	0.74 ± .07	0.92 ± .20	0.41 ± .05
Operation	60-120	1.32 ± .28	1.96 ± .38	0.96 ± .11
S/P Biliary	0-60	2.14 ± .33*	4.66 ± .53*	1.69 ± .26*
Duct Ligation	60-120	2.84 ± .17*	10.01 ± .99*	3.90 ± .18*

* Significantly different from "sham" operated, $P < 0.05$ by unpaired Student's t-test

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TABLE 4-7

Effect of Bilateral Nephrectomy on Biliary Excretion of Ketamine and Its Metabolites under Halothane Anesthesia

The rates of biliary excretion for ketamine and metabolites I and II in control ("sham operated") and nephrectomized rats under 0.8% halothane anesthesia were compared as detailed under "Materials & Methods." Values represent means ± S.E.M. for four animals.

	Time interval (min.)	Rate of Biliary Excretion (µg/min)		
		Ketamine	Metabolite I	Metabolite II
S/P Sham Operation	0 - 30	4.44 ± 0.38	9.44 ± 0.42	2.12 ± 0.64
	30 - 60	6.88 ± 0.66	15.80 ± 0.80	3.68 ± 0.48
	60 -120	4.60 ± 0.64	13.70 ± 0.50	3.92 ± 0.70
S/P Bilateral Nephrectomy	0 - 30	6.26 ± 0.50	11.12 ± 0.44	1.92 ± 0.30
	30 - 60	10.42 ± 0.80	19.20 ± 0.72	3.72 ± 0.74
	60 -120	7.34 ± 0.68*	17.60 ± 0.54*	4.12 ± 0.82

* Significantly different from "sham" controls, $P < 0.05$ by unpaired Student's t-test

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nephrectomized animals. The plasma and brain levels of ketamine and metabolite I in the two groups appeared to reflect these changes as the initial levels were not altered following the nephrectomy; however, the slopes of the decay curves were reduced by blocking urinary excretion (unreported data).

DISCUSSION

Our earlier studies indicated that halothane altered the biodisposition of ketamine when the two drugs were administered concurrently. Interactions of halothane with diazepam (Kanto & Pihlajamaki, 1973) and pentobarbitone (Pearson et al, 1973) have been shown to prolong plasma half-lives of the latter drugs. On the other hand, Rahn et al. (1969) reported on the lack of effect of halothane on the metabolism of thiopental. We have found that halothane prolongs ketamine's half-life and that this prolongation of plasma, and hence brain, half-life values produced corresponding changes in the duration of ketamine-induced ataxia (fig. 4-1). The levels of ketamine in plasma and brain tissue at the termination of the ataxic period were of similar magnitude in both control and halothane-treated groups. Because halothane-induced alterations in the pharmacologic actions of ketamine were coincident with changes in its disposition, we attempted to ascertain the mechanism(s) underlying such effects.

Previous investigators have suggested that the biodisposition of ketamine may be analogous to the ultrashort-acting barbiturates because of its rapid onset of action, short duration of hypnosis, and high lipid solubility (Dundee, 1971; Cohen et al., 1973; Chang & Glazko, 1974; Cohen & Trevor, 1974). Our studies of the uptake and distribution of parenterally administered ketamine (figs. 4-3 & 4-5) show that the distribution and redistribution of ketamine is similar to that for thiopental (Price et al, 1959; Goldstein & Aronow, 1960). In the case of ketamine the time course of such events is reduced, perhaps due to the fact that ketamine is five-to-ten times more lipid soluble than the thiobarbiturate (Mayer et al, 1959; Cohen & Trevor, 1974). Ketamine is rapidly distributed to the vessel-rich group of tissues (e.g. brain, heart and kidney);

equilibrium was approached more slowly in skeletal muscle and, finally, drug that had reentered the blood from the vessel-rich group of tissues was redistributed to fat and skin/subcutaneous tissue which were last to equilibrate with the falling plasma level. Our data agrees with the two-compartment model of Wieber et al (1975) where the α-phase has a plasma half-life of 10-20 minutes and the β-phase corresonded to a plasma half-life of 2-3 hours depending on the route of administration. Thus, the α-phase of the plasma decay curve is brought about mainly by the processes of distribution and redistribution between the central and peripheral compartments, while the β-phase reflects final elimination and is due predominately to drug metabolism and excretion.

These data on the biodisposition of ketamine and its principal metabolites following i.m. ketamine administration (figs. 4-3 & 4-4; table 4-2) demonstrate that halothane slows the uptake, distribution and redistribution of ketamine as well as slowing the distribution of metabolite I. The delay in attainment of peak plasma levels after i.m. ketamine may be due to direct actions of halothane at the level of muscle perfusion. The delays in the distribution of ketamine, metabolite I and metabolite II to other tissues, as well as slowed redistribution of ketamine, could also be due to hemodynamic actions of halothane, including a decrease in cardiac output (Goldberg, 1968; Eger et al, 1970). Based on computer model studies, a decrease in blood flow at the site of an intramuscular injection of thiopental had been postulated to slow drug uptake and reduce peak brain levels, while elevating subsequent levels in the brain (Saidman & Eger, 1973). This postulate is supported by our in vivo experimental results in rats. One relatively unexpected finding was that halothane appeared to increase the in vivo tissue/plasma ratios at the time of attainment of peak tissue levels (table 4-1). These values probably most closely represent the true tissue/plasma partition partition coefficients since there is no net flux of drug at the peak point (i.e., a transient equilibrium is reached). If this finding is correct, it would also contribute to slowing the redistribution of ketamine in the presence of halothane. This effect would delay attainment of peak levels and also increase the plasma and tissue half-lives.

Since effects of halothane on the disposition of ketamine after i.m. administration might have resulted simply from a reduction in the rate of absorption of ketamine from muscle into plasma, it was necessary to evaluate the distribution and redistribution of ketamine after the i.v. route of administration under halothane anesthesia. The disposition of intravenously administered ketamine (figs. 4-5 & 4-6) was similar to that discussed previously after i.m. injection, with the amount of drug going to any one tissue being roughly proportional to the tissue blood flow. Although initial tissue levels were not significantly altered by halothane anesthesia, elevated levels of ketamine were found in plasma, brain and muscle at later time intervals. Thus, halothane-induced changes in plasma and brain half-lives of ketamine were not simply due to a decreased rate of ketamine absorption from the i.m. site of administration. These data also indicate that halothane produces differential alterations in organ perfusion, slowing the redistribution of ketamine and the distribution of metabolite I from the liver and other vessel-rich tissues as evidenced by significantly lower levels of ketamine and metabolite I in skin/subcutaneous tissue. The slow time constant for ketamine in this lipid-rich tissue is related to its high tissue solubility, requiring more time to reach equilibrium. Although the major effect of halothane in prolonging ketamine tissue half-life values might have resulted from depression of the cardiovascular system, it was also possible that halothane, which has been shown to have inhibitory effects on hepatic N-demethylation and glucuronide conjugation (Brown, 1971 & 1972), could exert an inhibitory influence on the biotransformation of ketamine.

Halothane was found to produce reversible, concentration-dependent decreases in the rate of ketamine degradation in vitro (table 4-3; fig. 4-7). The noncompetitive nature of the halothane-induced inhibition of ketamine metabolism (figs. 4-8 & 4-9) is consistent with the findings of Brown (1971 & 1972) with regard to effects of halothane on hepatic metabolism of drugs like hexobarbital, aminopyrine and p-nitrophenol. Since these drugs are classified as type I substrates for microsomal mixed-function oxidase, we would predict that ketamine is also a type I substrate. In the present study, halothane effects on the in vitro biotransformation of ketamine occurred at lower concentrations of the gas anesthetic than reported in previous studies, i.e. halothane concentrations employed in this study were in the clinically useful range. Halothane also decreased the in vitro rate of disappearance of metabolite I in a noncompetitive fashion (fig. 4-10), although the maximal rate of this reaction was significantly slower than the N-demethylation reaction.

Since we are unable to account for the degradation of ketamine or metabolite I completely in terms of metabolite I and metabolite II formation, it would appear likely that additional metabolites were formed which were not detected by our gas-liquid chromatographic analysis. The ketamine metabolites shown on figure 2-1, namely metabolites III (6-(hydroxyl-2-(o-chlorophenyl)-2-(amino)cyclohexanone) and IV (5-(hydroxyl)-2-(o-chlorophenyl-2-(amino)-cyclohexanone), as well as their glucuronide conjugates, have been detected by thin-layer chromatography (Chang & Glazko, 1974).

The overall rate of in vivo metabolism was assessed in the presence of halothane anesthesia (table 4-4) and the results were consistent with either a direct inhibitory effect of halothane on ketamine biotransformation or a halothane induced reduction in hepatic blood flow (Epstein et al, 1966). The latter possibility would only be important if metabolism followed first-order kinetics and would be compensated for, at least in part, by increased blood levels of ketamine. Saidman & Eger (1966) reported that there were no significant changes in the amount of thiopental metabolized in hypovolemic subjects during halothane anesthesia. They found that the effects of reduced hepatic blood flow were offset by higher absolute plasma concentrations of the drug. Our inability to completely account for the amount of drug administered in terms of measured levels of ketamine, metabolite I and metabolite II also would be consistent with the formation of additional metabolites as described above. The increased overall recovery in the presence of halothane anesthesia also might indicate that halothane was decreasing the rate of formation of these other metabolites. The inhibitory effect of halothane on the metabolism of ketamine might be expected to contribute to a prolonged elevation of plasma ketamine levels. Finally, any reduction in the rate of excretion of the drug would also tend to increase plasma and hence brain half-life values of ketamine.

Since the major portion of ketamine and its metabolites are recovered from the urine (Chang & Glazko, 1974), we determined the effect of halothane on urinary excretion of these compounds. Although the urine output was decreased secondary to halothane-induced cardiovascular depression, urinary excretion of ketamine was not significantly changed during halothane anesthesia (table 4-5). Furthermore, nephrectomy did not alter the initial tissue distribution or redistribution of ketamine, however the slope of the β-phase of the plasma decay curve was was reduced in a predictable fashion and biliary excretion was enhanced at later time intervals (table 4-7). Ligation of the bile duct, on the other hand, produced significant changes in the biodisposition of ketamine and its metabolites as well as enhancing its rate of urinary excretion (table 4-6). These studies would tend to confirm the hypothesis that urinary excretion is of minor importance in the initial biodisposition of ketamine. Furthermore, although significant quantities of ketamine and metabolites I and II were secreted into the bile, the fecal route of excretion is normally of minor significance in the overall biodispostion of ketamine because of the rapid reabsorption and enterohepatic recirculation of these highly lipid-soluble compounds. The effects on ketamine biodisposition following biliary duct ligation are most likely related to blockade of biliary excretion rather than altered hepatic metabolism since the effects of 2-3 hours of biliary duct occlusion on hepatic parenchymal function, as reflected by abnormally elevated liver function tests, is trivial (Breen et al, 1973). The markedly elevated brain and plasma levels of ketamine seen following biliary ligation might have clinical relevance in patients undergoing operations for cholelithiasis or biliary tract obstruction secondary to cholangiocarcinoma, pancreatic carcinoma or chronic pancreatitis. In these clinical situations enhanced urinary excretion would tend to compensate for the reduced biliary clearance; however, in the presence of reduced renal function the maintainence doses of ketamine would have be reduced and/or the dosing interval lengthened.

In conclusion, it would appear that the major effects of halothane on ketamine biodisposition, which result in prolongation of the pharmacologic effects of the latter drug, include changes in uptake and distribution processes via hemodynamic actions as well as decreases in the rate of hepatic degradation of the drug. Our results suggest that the inhalation anesthetics which affect the cardiovascular system and impair hepatic metabolic function may alter the disposition of another drug given concomitantly. This type of interaction prolongs the effects of a fixed agent like ketamine and may contribute to a protracted recovery from its postanesthetic actions on the central nervous system.

SUMMARY

Ketamine, a highly lipophilic drug, was rapidly distributed into highly vascular organs and subsequently redistributed to less-well perfused tissues, with concurrent hepatic metabolism and urinary and biliary excretion, after both i.m. and i.v. administration. Halothane, a potent cardiovascular depressant, was found to prolong the plasma and brain half-life of ketamine and also increased the duration of ketamine-induced ataxia when the two drugs were administered concomitantly. Halothane anesthesia (0.8% halothane in oxygen) produced a decrease in the rate of uptake and delayed distribution and redistribution of ketamine (50 mg/kg i.m.), while the rate of urinary excretion of ketamine was not significantly altered. Similarly, redistribution of intravenously administered ketamine (30 mg/kg i.v.) was slowed in the presence of halothane. _In vitro_ hepatic microsomal metabolism of ketamine and metabolite I was inhibited noncompetitively by halothane with inhibitor constants (Ki) for halothane estimated to be 1.56 and 1.64 mM, respectively. The gas anesthetic also decreased the overall rate of _in vivo_ metabolism of ketamine (30 mg/kg i.v.) in a concentration-dependent manner.

Halothane anesthesia, by decreasing uptake, distribution, redistribution and metabolism of ketamine, produced significant prolongation of ketamine's pharmacologic actions on the CNS. Although urinary and biliary excretion probably play a minor role in ketamine's initial biodisposition, impaired renal function and/or biliary obstruction may produce alterations in ketamine's pharmacokinetics and thereby alter its action. Our results imply that concomitant use of inhalational anesthetics may prolong pharmacologic actions of other agents via effects on distribution/redistribution processes as well as on metabolism.

APPENDIX

DETERMINATION OF ANESTHETIC REQUIREMENT

DETERMINATION OF ANESTHETIC REQUIREMENT

Rats have been used to study the effects of circadian rhythm (Munson et al, 1970), temperature (Munson et al, 1970; Vitez et al, 1974) and other drugs (Munson et al, 1968; Miller et al, 1968; Vitez et al, 1973; Mueller et al, 1975) as well as anesthetic combinations (DiFazio et al, 1972) on minimum alveolar concentration (MAC) of anesthesia. In addition to these variables, other factors factors such as respiratory depression and age may affect this ED50 of anesthesia. Previous studies have measured the inspired anesthetic concentration and then assumed the equality of inspired and alveolar anesthetic gas tensions. The validity of this assumption is increasingly doubtful for anesthetics of moderate (e.g. halothane) to high (e.g. methoxyflurane) solubility, particularly if these anesthetics concomitantly cause hypoventilation. Any inspired-to-alveolar anesthetic concentration gradient may be accentuated by increased airway obstruction and/or medullary depression. To accurately determine anesthetic requirement, measurement of alveolar anesthetic tension is necessary because it closely reflects the partial pressure of anesthetic gas in the brain.

A difference between inspired and alveolar gas concentrations would invalidate previous "MAC" determinations in rats. Using halothane and a new less-soluble anesthetic, isoflurane, we conducted the following study to ascertain the quantitative error in MAC produced by using inspired rather than alveolar anesthetic concentrations. We studied the time course for equilibration of these anesthetic agents, and indirectly studied the contribution of respiratory obstruction to the differences between inspired and alveolar gas tensions. Finally, since age has a significant effect on anesthetic requirement in man, we determined what effect age had on ED50 values of anesthetics in rats.

MATERIALS & METHODS

Male Sprague-Dawley rats were divided into four groups. Anesthesia in the first two groups was induced and maintained with a halothane-oxygen mixture. The first halothane group (H-1) consisted of twenty rats, 290 ± 10 g in weight and 3.5 ± 0.5 months old. The second halothane group (H-2) differed from group H-1 in weight (540 ± 20 g) and age (8.0 ± 0.5 months). In the two remaining groups (I-1 and I-2), anesthesia was induced and maintained with isoflurane in oxygen. Group I-1 consisted of twenty-two rats weighing 290 ± 10 g and 3.5 ± 0.5 months of age, while group I-2 differed in weight (540 ± 20 g) and age (8.0 ± 0.5 months).

The rats were anesthetized in a clear cyclindrical chamber, 25 cm in length and 8 cm in diameter. Halothane or isoflurane was vaporized by directing 100% oxygen through a 250 ml gas washing bottle, and this was then directed to a reservior connected to the anesthesia chamber. Samples were drawn for measurement of anesthetic gas concentrations from the inflow line distal to the reservior and from catheter(s) inserted into the end of the chamber; one of the latter catheters was connected to the endotracheal device and used to obtain "alveolar" gas samples. Pure alveolar gas samples are impossible to obtain; therefore, end-tidal (i.e. end-inspiratory) samples were measured and these were assumed to be indicative of alveolar gases. A schematic representation of our experimental apparatus is illustrated in figure 5-1. An intravenous extension tube (Pharmaseal, type K-50) reduced to 4 cm in length served as the tracheostomy tube. The endotracheal device was inserted into a tracheostomy in eight rats of each group. A small connector with a side-arm sampling tube and a 1 ml dead space was attached to the end of the tracheostomy tube. The

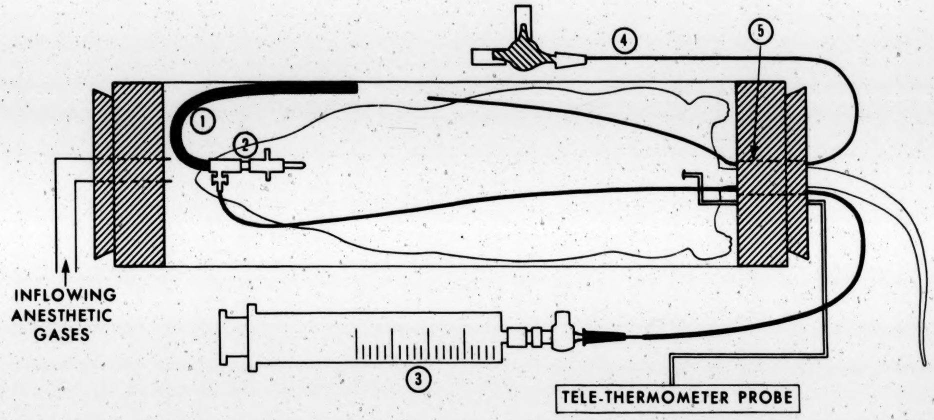

Figure 5-1. Schematic representation of a tracheostomized rat in a plastic experimentation chamber. Other aspects of the apparatus include; (1) respiratory dead space tubing, (2) tracheostomy tube and connector with end-expiratory gas sampling catheter attached, (3) glass syringe used to obtain "alveolar" gas samples, (4)chamber sampling catheter used to obtain inspired gas samples, and (5) opening through which the tail, gas sampling catheters, and outflowing anesthetic gas passes to the outside.

The purpose of the external dead space was to replace the "physiological dead space" lost as a result of the tracheostomy. Additionally, the dead space made it possible to obtain end-tidal gas samples which would be less contaminated with inspired gases. To obtain an end-tidal anesthetic sample, 20 to 30 consecutive 0.5 ml end-expiratory gas samples were collected manually from the side arm sampling line of the tracheostomy tube in a 20 ml glass syringe. End-expiratory gas samples and inspired (i.e. chamber) anesthetic samples were immediately analyzed with Beckman LB-1 infrared analyzers for carbon dioxide and either halothane or isoflurane. All readings were made at ambient pressure. Rectal temperature was monitored and maintained at 37 ± 1° C with a heating blanket.

The ED50 of anesthesia was the anesthetic gas tension midway between the concentrations permitting and preventing movement in response to a clip applied to the distal one-third of the tail for one minute. The technique is similar to the method of determining MAC in dogs as originally described by Eger et al (1965). The force applied did not produce injury to the tail yet inflicted a maximal stimulus as evidenced by the fact that additional pressure did not increase the ED50 values. Following each change in the inspired concentration, 25-35 minutes were allowed for stabilization of the alveolar gas concentration. The ED50 values, determined from 2 to 3 hours following induction, were obtained in three different ways. Initially, we determined an "inspired ED50" based on chamber anesthetic gas concentration in rats without tracheostomies. In addition, eight rats in each of the four groups were reanesthetized with the same anesthetic agent twenty-four hours after their inspired ED50 values had been determined without a tracheostomy; and then, following completion of the tracheostomy "inspired ED50" and "aveolar ED50" (or MAC) values were determined by simultaneously sampling both chamber and end-tidal gas concentrations.

Statistical methods:

Mean ED50 values were tested for statistical significance using analysis of variance and linear combinations with $P < 0.05$ indicative of significance. Ratios of inspired-to-alveolar anesthetic gas concentrations were determined and related to the duration of anesthesia. Data points were derived by averaging each group of inspired-to-alveolar ratios obtained from anesthetic gas samples drawn during the same ten-minute time intervals after completion of the tracheostomy. Curves to fit these relationships for halothane and isoflurane were derived by curvilinear regression analyses.

Chemicals:

Halothane (Fluothane) used in these experiments was generously supplied by Ayerst Laboratories Inc (New York, NY), while isoflurane (Forane) was provided by Ohio Medical Products, Division of Airco Inc (Madison, Wisc).

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RESULTS

The ED50 values obtained measuring anesthetic gas tension in three different manners during halothane or isoflurane anesthesia were compared using bar grafts (figs. 5-2 to 5-4). In all groups the inspired ED50 values in rats without tracheostomies were found to be significantly greater than their respective alveolar ED50 or MAC values. For example, in group H-1, the inspired ED50 was 14% higher than MAC (i.e. 1.26% halothane versus 1.11% halothane). There also were differences between ED50 values obtained in rats with tracheostomies depending upon whether inspired or alveolar gas tensions were measured and these differences were found to be greater during halothane anesthesia. The inspired ED50 values in non-tracheostomized rats were greater than the values for inspired ED50 in those same animals with tracheostomies. The differences between inspired ED50 values with and without tracheostomies were found to be greater during isoflurane anesthesia and consistently larger for the older than the young rat groups. The inspired ED50 values for rats without tracheostomies demonstrated no significant differences between the young and old groups of rats. However, when tracheostomies were performed, inspired ED50 and MAC values for young rats were significantly greater than the corresponding values for the older group of rats (fig. 5-5).

Mean alveolar carbon dioxide values during halothane and isoflurane anesthesia are reported in table 5-1 as a function of MAC-multiples. During halothane anesthesia, the partial pressures of carbon dioxide ranged from 45-54 torr with end-tidal anesthetic concentrations ranging from 0.65-1.40% halothane in oxygen. While during isoflurane anesthesia, the alveolar carbon dioxide tensions ranged from 44-53 torr with aveolar anesthetic gas tensions

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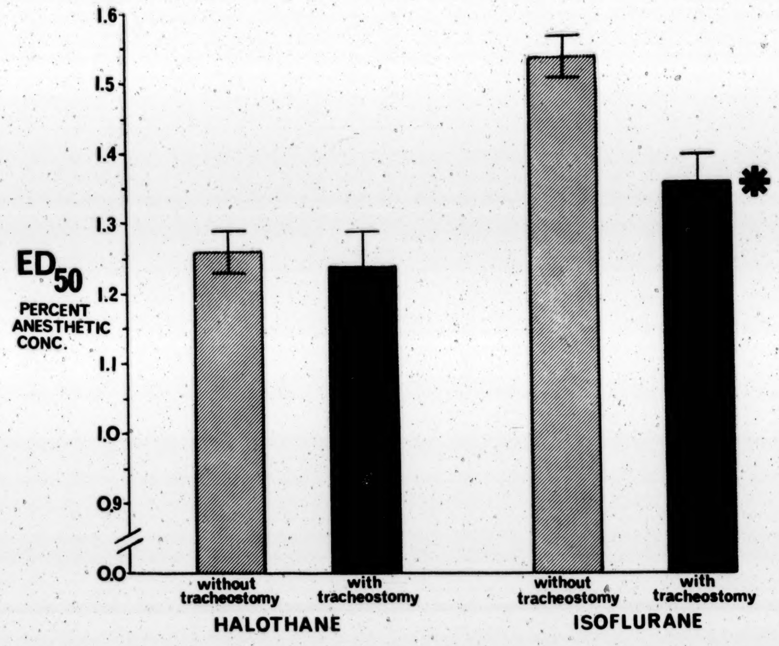

Figure 5-2. Comparisons of "inspired ED50" values in young rats with and without tracheostomy tubes under halothane or isoflurane anesthesia. Asterisk (*) indicates significant difference, with P 0.05 by paired Student's t-test. Values represent means ± S. E. M.

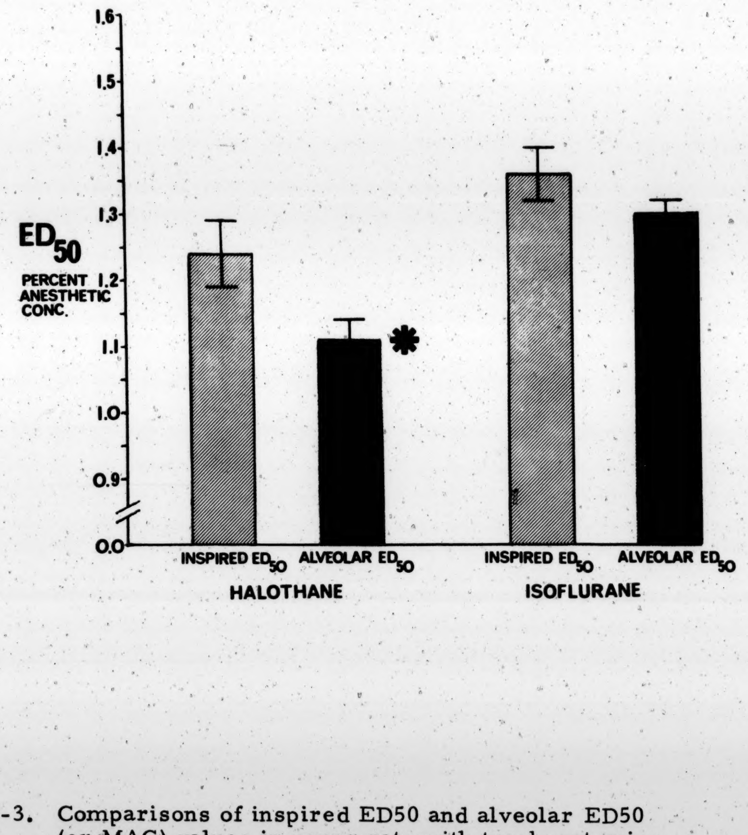

Figure 5-3. Comparisons of inspired ED50 and alveolar ED50 (or MAC) values in young rats with tracheostomies under halothane or isoflurane anesthesia. Asterisk (*) indicates significant difference, with P 0.05 by paired Student's t-test. Values represent means ± S.E.M.

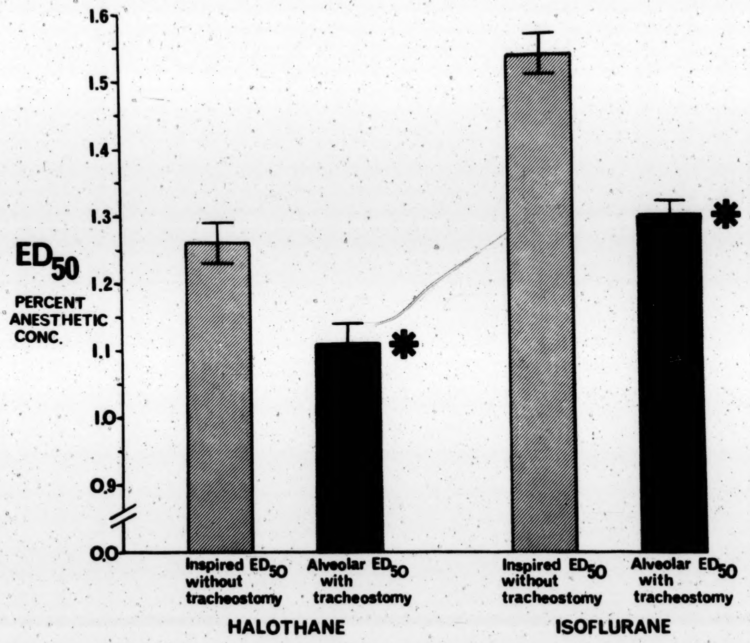

Figure 5-4. Comparisons between inspired ED50 values in non-tracheostomized young rats and alveolar ED50 (or MAC) in the same animals after tracheostomization under halothane or isoflurane anesthesia. Asterisk (*) indicates significant difference, with P 0.05 by paired Student's t-test. Values represent means ± S.E.M.

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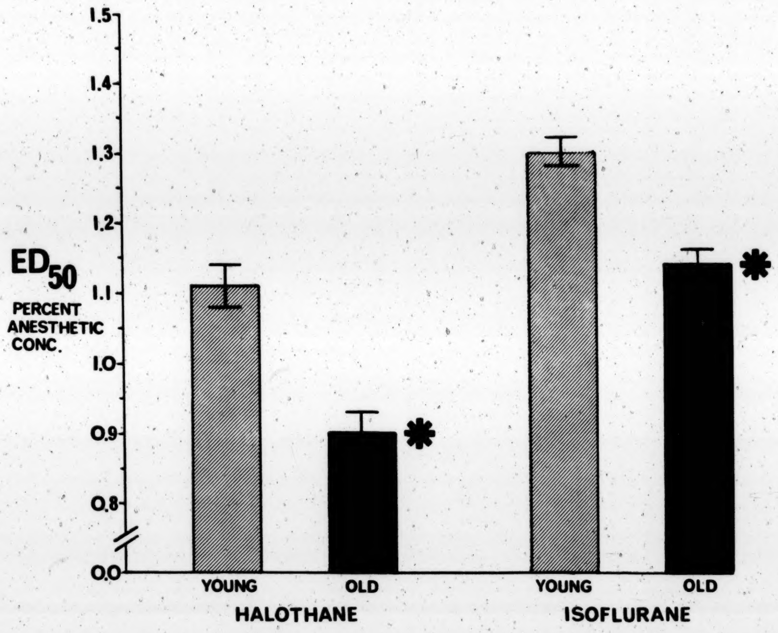

Figure 5-5. Effect of age on alveolar ED50 (or MAC) during halothane and isoflurane anesthesia. Asterisk (*) indicates significant difference, with P 0.05 by unpaired Student's t-test. Values represent means ± S. E. M.

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TABLE 5-1

Partial Pressures of Carbon Dioxide in the End-Expiratory Gas Samples during Halothane and Isoflurane Anesthesia

End-tidal (alveolar) carbon dioxide tensions were measured in tracheostomized spontaneously breathing rats under various concentrations of halothane or isoflurane as detailed in the section on "Materials & Methods." The carbon dioxide levels (torr) were compared at equi-potent concentrations of the two anesthetics (i. e equal MAC-multiples). Values are means ± S. E. M. of the samples collected (#) at a given concentration of the anesthetic.

MAC-Multiples	Halothane				Isoflurane			
	Group H-1		Group H-2		Group I-1		Group I-2	
	#	CO2	#	CO2	#	CO2	#	CO2
0.75 x MAC	50	46 ± 2	58	45 ± 1	12	45 ± 3	10	44 ± 3
1.00 x MAC	32	50 ± 1	50	46 ± 2	8	50 ± 4	8	46 ± 3
1.25 x MAC	12	54 ± 2*	22	50 ± 2*	8	53 ± 3*	7	52 ± 4*

* Signficantly different from end-tidal carbon dioxide tensions at 0.75 x MAC, $P < 0.05$ by unpaired Student's t-test.

from 0.90-1.75% isoflurane in oxygen. Thus, end-tidal carbon dioxide levels during halothane and isoflurane anesthesia were essentially the same at equipotent doses (i.e. at the same MAC-multiples). Although the differences in partial pressure of alveolar carbon dioxide were not large, there was a suggestion of dose-dependent increases in end-expiratory carbon dioxide tension as a function of the anesthetic concentration.

The ratio of inspired-to-alveolar halothane or isoflurane progessively decreased with increasing duration of anesthesia (fig. 5-6). Furthermore, two-to-three hours after initiating the induction period with a high anesthetic gas concentration, the inspired-to-alveolar differences for halothane were still approximately 9-13%, while the differences for isoflurane were only 3-6%.

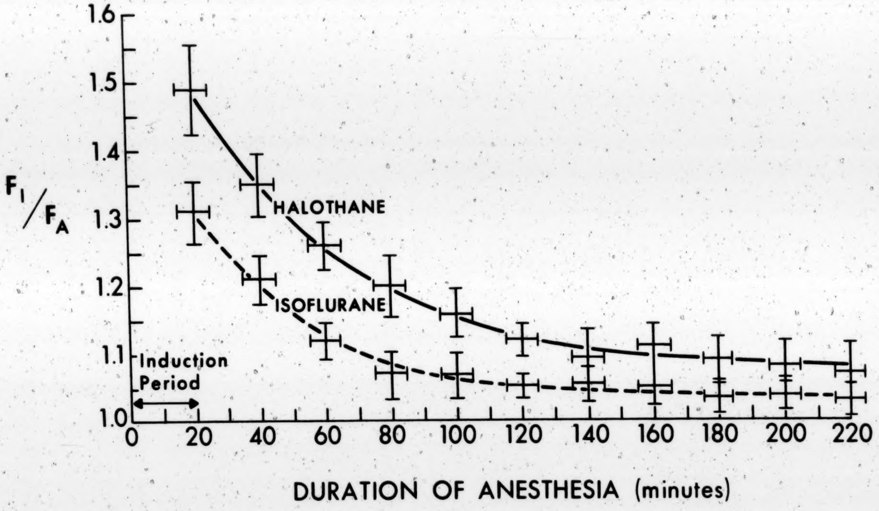

Figure 5-6. Effects of the duration of halothane (├───┤) and isoflurane (├-------┤) anesthesia on the ratio of inspired-to-alveolar anesthetic gas tension. Values are means for 10-15 samples at each time interval and the brackets represent ± S.E.M.

DISCUSSION

Our results demonstrate that inspired gas concentrations do not equal alveolar anesthetic gas tensions of halothane or isoflurane, even in the presence of a tracheostomy. Our mean inspired ED50 value for halothane in normal young spontaneously breathing rats without tracheostomies agreed with the "halothane MAC" values (1.26-1.29%) reported by other investigators using inspired gas measurements (Munson et al, 1970; Munson, 1970). We have also found that using inspired gas samples as an indicator of halothane or isoflurane anesthetic requirement will give falsely elevated values. Thus, MAC for any moderately or highly soluble anesthetic agent should not be determined from inspired gas samples.

As anticipated from its lower blood solubility (i.e. lower blood/gas partition coefficient), inspired-to-alveolar isoflurane concentration ratios were smaller than the ratios for halothane, where the blood/gas partition coefficient in rats has been reported to be 6.6 (Wahrenbrock et al, 1974). These data (fig. 5-6) suggest that a further decrease in the solubility of an anesthetic agent in blood would allow the substitution of inspired for alveolar anesthetic concentrations. This suggestion is supported by the finding that the inspired-to-alveolar ratios for cyclopropane in tracheostomized rats approach unity within the first thirty minutes of anesthesia (Vitez et al., 1973). Similarly, our data suggest that that although significant inspired-to-alveolar isoflurane differences appear in the rat, such differences might be negligible in the mouse (or other small mammal) where the ventilation per kilogram of body tissue is extremely high and uptake has less influence on the alveolar rate of rise (Eger et at, 1971).

The importance of ventilation also is suggested by our demonstration of higher inspired ED50 values in rats without tracheostomies than was found in those same animals in the presence of a tracheostomy. Rats without tracheostomies often appeared to be partially obstructed and this was more evident subjectively in those rats anesthetized with isoflurane. We speculate that the higher inspired ED50 was caused by a reduced alveolar ventilation produced both through medullary depression and by increased airway obstruction. All inhalational anesthetic agents depress cardiac output as well as ventilation (Black & McKane, 1965; Restall et al, 1966; Price, 1975), and consequently reduce inspired-to-alveolar differences. The depression of cardiac output only is found when ventilation is controlled, since the increased carbon dioxide tension associated with spontaneous ventilation apparently maintains the cardiac output via sympathetic stimulation. Furthermore, halothane and isoflurane depress alveolar ventilation to a greater extent than they depress cardiac output (Munson et al., 1973). Thus, even with minimal decreases in cardiac output, increased airway obstruction may result in much larger inspired-to-alveolar differences than would otherwise be predicted.

Although indicating modest respiratory depression, our alveolar carbon dioxide tensions obtained from tracheostomized rats were not elevated sufficiently to exert narcotic effects (Eisele et al, 1967). In a separate group of five tracheostomized rats, arterial blood carbon dioxide levels were compared to alveolar carbon dioxide values obtained at the same time while under halothane anesthesia (with concentrations ranging from 0.75xMAC to 1.25xMAC). Our arterial blood carbon dioxide values were found to be 10-12% greater than the corresponding alveolar carbon dioxide tensions (unreported data). These results as well as the magnitude of our alveolar carbon dioxide values (table 5-1) would suggest that our end-expiratory anesthetic gas samples approximated alveolar samples. If significant contamination of alveolar samples with inspired gas had occurred, arterial-to-alveolar carbon dioxide differences should have been larger as the inspired gas would have appreciably diluted the end-tidal carbon dioxide values. Our arterial-to-alveolar carbon dioxide differences of 10-12% were comparable to those obtained by Nunn & Hill (1960) in spontaneously breathing anesthetized patients. Nevertheless, our inspired-to-alveolar differences would represent underestimates since some mixing of inspired and alveolar gases in all probability was occurring.

In order to reduce any variation in the anesthetic requirement due to circadian rhythm (Munson et al, 1970), the ED50 determinations in rats with tracheostomies were performed twenty-four hours after the inspired ED50 values had been determined in the same rats without tracheostomies. At the outset of the study, in separte groups of five rats each, inspired ED50 determinations in non-tracheostomized rats during halothane and isoflurane anesthesia were repeated after a twenty-four hour time period and we did not find any significant changes for either the young or the old groups of rats (unreported observation).

Our results in rats agreed with the inverse relationship between age and anesthetic requirement demonstrated in man (Gregory et al, 1969; Nicodemus, 1969; Stevens et al, 1975). These data suggest that comparisons of MAC values must account for age differences if they exist. Similarly, age variability also may lead to increased variability in determinations of anesthetic requirement.

In order to successfully use the rat as an experimental model in studying inhalational anesthetic agents, the age of the animal as well as the solubility of the agent must be considered unless alveolar gas tensions are measured. Additionally, with some relatively insoluble or moderately soluble anesthetics like isoflurane, equilibrium between inspired and alveolar gas tensions may not be readily attained because of factors such as partial mechanical airway obstruction or excessive secretions.

SUMMARY

Measurement of anesthetic requirement based on inspired anesthetic gas concentrations assumes equilibration with alveolar, and consequently brain, anesthetic gas tensions. This assumption may be rendered invalid by the solubility of the anesthetic agent and its effects on ventilation. To test this hypothesis, ED50 values of anesthesia using halothane (H) and a less-soluble anesthetic, isoflurane (I), were determined in rats with and without tracheostomies. Alveolar ED50 or MAC values for H and I were 1.11 ± 0.03% and and 1.38 ± 0.02%, respectively. Inspired ED50 values determined from two-to-three hours after induction of either halothane or isoflurane anesthesia in non-tracheostomized rats were 14% and 17% greater, respectively, than alveolar ED50 values determined at the same time interval following tracheostomization. These data demonstrate that previous studies in which halothane anesthetic requirement was determined using inspired gas samples are inaccurate. Inspired ED50 values for halothane and isoflurane in rats without tracheostomies were 2% and 11% greater, respectively, than the inspired ED50 values in those same animals with tracheostomies. Even after three hours of anesthesia in tracheostomized rats, measurements of inspired-to-alveolar differences in anesthetic gas tension revealed 9% and 3% diferences for halothane and isoflurane, respectively. Thus, the use of inspired concentrations in rats is limited to those inhalational anesthetics with low blood/gas partition coefficients and with minimal effects on ventilation. A moderate or highly soluble anesthetic agent or one which results in significant respiratory depression requires the direct measurement of "alveolar" anesthetic gas tension to determine anesthetic requirement.

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